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General Charles James Fox, M. D.
HARTFORD, CONN.

TRANSACTIONS OF THE

SECTION ON

Practice of Medicine

of the
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at the Fifty-eighth Annual
Session, held at Atlantic
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THE EARLY OR PREMONITORY SYMPTOMS OF PERNICIOUS ANEMIA.

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As far as we now know, pernicious anemia is the result of a toxemia. The symptoms and course of the diseases are clearly in accord with this, and the study of the bothriocephalus anemias permits scarcely any other conclusion. What the exact nature of this toxin is is still a matter of speculation and doubt. It is generally agreed, however, that its origin is somewhere in the alimentary canal. The study of the bacteria in the intestinal canal has gone far towards establishing this consensus. In a recent publication by Dr. C. A. Herter, it is definitely shown, for instance, that the *B. aerogenes capsulatus* is an active hemolytic agent, and that when the *B. coli* type is sufficiently meager to permit a very large and free growth of the *B. aerogenes* alterations in the blood gradually appear and ultimately the blood picture of either a secondary or a pernicious anemia arises. Although experimental pernicious anemia, by producing *B. aerogenes* infection of the intestinal canal has not yet been brought about, the evidence of a causal relation is as strong as in the bothriocephalus anemias. In a number of cases collected by Herter, the typical blood picture of pernicious anemia was present, while the *B. aerogenes* held full sway in the intestinal canal and disappeared as this particular bacillus disappeared and the usual intestinal flora returned.

At present, as has been in the recent past, the diagnosis of pernicious anemia is based almost entirely on the blood picture, such as a high color index, megaloblasts, megalocytes, poikilocytes and leucopenia. If our present conception of this disease is correct, this striking blood change is due to a toxemia. This blood change is not the cause of the symptoms which may have preceded it or which followed. It is simply a part of the symptom-complex of pernicious anemia, and is at present looked on as pathognomonic. Other prominent symptoms are, as is well known, loss of muscular power, dyspnea and cardiac oppression, a peculiar pallor, edema, subcutaneous and submucous hemorrhage, loss of appetite, achylia, diarrhea or alternate diarrhea and constipation, a peculiar odor of the breath, eye symptoms, and certain nervous manifestations, such as tabes dorsalis or peripheral neuritis.

The object of this paper is to consider the order or sequence of these symptoms, whether there is any definite regularity of their appearance, whether the characteristic blood changes are sufficiently marked to be detected before the major symptoms arise, or, if they are not, whether there is a group or complex of premonitory symptoms on which a diagnosis could be safely established before the so-called pathognomonic blood signs can be found.

From the literature of this subject, especially that which has arisen since the recognition of the bothriocephalus anemias, it is evident that there is no recognized regularity in the order of the appearance of the symptoms. Some may appear long before the typical blood picture can be detected. In one case one lesion may appear first, in a second another, and in a third a group may appear suddenly, or, again, none may be found at all before the blood shows a decided suspicion of the actual condition.

Now and then cases have been reported as pernicious anemia to which exception was taken at the time, be-

cause of discrepancies in the blood, but usually the diagnosis was made absolute in a subsequent report. One such case especially was reported by Dr. F. P. Henry before the Association of American Physicians in 1900. In referring to this case later, when the blood findings had become positive, Dr. Henry says:[1] "The diagnosis of pernicious anemia is most firmly based on the *tout ensemble* of signs and symptoms, both positive and negative. The presence of megaloblasts is confirmatory of, but not indispensable to, the diagnosis. They possess a prognostic rather than a diagnostic value, for they often appear in the blood in large numbers shortly before death, and are often absent for months during periods of remission." It is this statement, together with the fact that I have often in my own cases, especially during remission, found only "trifling anomalies of the blood," while grave symptoms could be easily elicited, that emphasized the necessity of considering more closely the early or premonitory symptoms of pernicious anemia. These symptoms seem to group themselves under those belonging to the digestive system, those of the nervous system and those of the cardiovascular system.

The relation of pernicious anemia and achylia gastrica has long been recognized. Their etiologic relation has been a matter of dissension since Flint's original observation. In a paper read by Stockton before this Association at this place in 1904, the discussion was properly closed by concluding that achylia gastrica is not an etiologic factor. I wish to refer to it again, however, as being a rather frequent symptom, and sometimes a very early symptom. Of the twenty cases which have come under my observation, achylia gastrica and its associated diarrhea were present in fourteen. In nine it was a very early symptom. In one of these cases it seemed to have been present thirty-five years before the blood condition was recognized, and in one remark-

1. Philadelphia Medical Journal, June 22, 1901.

able case, which I shall report briefly, it was present eight years before the blood changes appeared.

Mrs. J. H. C., aged 66 years, first consulted me in September, 1901. She then had an attack of diarrhea and vomiting which had come on suddenly without any apparent cause, and was persistent. The vomitus contained no free HCl. The hemoglobin was 75 per cent., and the R. B. C. 3,600,000. The patient had had similar attacks during the previous six years. During the first attack, in 1895, she was very ill and consulted Dr. Max Einhorn of New York, who made a diagnosis of achylia gastrica, and suggested a course of treatment which resulted in apparently complete recovery. The blood, which was examined at that time by Dr. Einhorn, showed no evidence of pernicious anemia. In none of the attacks did the blood show any anomalies up to January, 1903. At this time the hemoglobin was 45 per cent. and the R. B. C. 1,680,000. The red corpuscles appeared unusually large. No megaloblasts were found. The patient now began to appear like a case of pernicious anemia, but not until May, 1903, was the pathognomic blood picture detected. Death occurred in June, 1903. At that time the hemoglomin was 10 to 15 per cent.; R. B. C. 744,000, and the leucocytes 1,300. Though Dr. Einhorn did not find any anomalies in the blood in 1895, and I did not find them until eight years later, the continuousness of the symptoms through the whole course makes it appear highly probable that the underlying cause of pernicious anemia was present from the first.

Another case which I saw in consultation with Dr. Harshberger of Lewistown, Pa., also shows that gastro-intestinal symptoms were present six years before the full blood picture appeared. A brief report is as follows:

Miss McC., aged 47 years, was seen first in August, 1905. She had had diarhea and vomiting at intervals for five years. The patient was anemic, and was thought by Dr. Harshberger to have pernicious anemia, as she had that appearance. A blood examination made at the time showed, however, the hemoglobin 40 per cent., R. B. C. 4,000,000, W. B. C. 13,800, no nucleated red corpuscles. Repeated examinations were made. The stomach contents after an Ewald test breakfast showed an absence of gastric juice. I was unwilling to make a diagnosis of pernicious anemia, and considered the case one of achylia gastrica. The patient made an apparently re-

markable recovery, but in January, 1906, when the symptoms returned, I had the opportunity of making another blood examination and found the hemoglobin 30 per cent., R. B. C. 1,330,000, W. B. C. 6,000, and after a long search a few nucleated reds. From this time on the patient became gradually worse and died in August, 1906. Here again the gastrointestinal symptoms were present long before the pathognomonic blood symptoms arose.

It must, of course, be remembered that the findings of a blood examination are only relative. The smallest droplet appears infinitesimal compared with the volume of blood in the human body, and it is not unlikely that blood changes are present long before it is possible to find them.

The early gastrointestinal symptoms in all of my cases were marked by their intermittency and their resistance to ordinary treatment. They usually recurred without any reasonable cause.

The nervous symptoms of pernicious anemia may appear very early in the disease or may only enter the group of terminal symptoms. Leichtenstern observed a group of cases in which the spinal disease was observed first, the pernicious anemia becoming manifest later. In six of my cases the nervous symptoms were marked, but in none were they the first to appear. Four presented decided symptoms of peripheral neuritis, and two the usual symptoms of tabes dorsalis. In one of these cases the symptoms of tabes appeared late and in the following order: loss of co-ordination, loss of pupillary reflex, disturbances of sensation, loss of knee jerks. The knee jerks disappeared a month before death. In the other case, the symptoms appeared early with the gastric symptoms and four years before the blood symptoms appeared. A report of this case is as follows:

Mr. J. V. S., aged 47, consulted me first in August, 1897. He was pale, had lost twenty-five pounds in the previous two months and had gastric symptoms which were rather characteristic of carcinoma of the stomach, but after a short course of treatment, in which the regulation of the diet was the principal feature, the symptoms disappeared. The blood at this

time showed the hemoglobin 73 per cent., and the R. B. C. 3,520,000. A year later I again saw the patient. He had done a year of hard work as pastor of a large congregation. He complained now of a numbness on the outer side of the left leg. The knee jerks were normal. The blood at this time showed a hemoglobin of 85 per cent., and R. B. C. 3,680,000. The gastrointestinal symptoms had about all subsided. I did not see the patient again until August, 1901. At this time the gastrointestinal symptoms were characteristic of achylia gastrica. The nervous symptoms, which had advanced slowly since 1898, were decidedly those of tabes dorsalis—absent knee reflexes, loss of co-ordination, girdle symptoms, pupillary disturbances and lightning pains. A history of lues was excluded, but there had been a severe postdiphtheritic paralysis at the age of 30. The blood now was hemoglobin 72 per cent., R. B. C. 4,008,000, but within six months the color index became high and poikilocytes and megalocytes appeared. The patient was under my observation for the following two years, during which time there were several marked remissions. In 1903 he went to the Pacific Coast, where he lived for two years, finally dying of pernicious anemia.

In this case I scarcely hesitated to make a diagnosis of pernicious anemia at least six months before the appearance of the blood warranted it. Here, again, it seems to me that the underlying cause of pernicious anemia was present from the beginning of the illness in 1898.

The cardiovascular symptoms of pernicious anemia are the least characteristic of the disease. The earlier ones can, therefore, be very easily overlooked or misinterpreted. They consist of palpitation, precordial distress, dyspnea, pulsation of the carotids, sleeplessness and anxiety, and later small hemorrhages, edema and nearly all the symptoms of failure of cardiac compensation. Practically all of these symptoms at one time or another were present in all of my cases, but in a few (five cases) such symptoms as precordial distress and dyspnea appeared early before the real condition was suspected and before the condition of the blood warranted a diagnosis. One of these is rather remarkable in that the precordial distress and peculiar color of the skin were the only symptoms, and only for a short in-

terval did the blood show that slight suspicion which revealed what seemed to me the real condition.

I report this case, though objection to my diagnosis may reasonably be taken.

Mr. G. W. B., aged 67, consulted me first in October, 1903. He complained of pain through the upper portion of the chest when walking, slight dyspnea, and of feeling unusually weak and tired. These symptoms had come on gradually during the previous six months; otherwise he felt perfectly well. His color made me suspicious of some form of anemia. The Hb was 64 per cent., and R. B. C. 3,040,000, possibly slightly irregular in size and shape—no nucleated reds were found. Physically he seemed perfectly well. There was a marked arcus senilis, but no retinal changes. His arteries were probably a little thick. The heart sounds and blood pressure were normal. The urine was normal. No intestinal parasites were recovered. I was unable to account for the substernal pain and distress; at the same time I could not entirely dismiss the idea of the presence of the early signs of pernicious anemia. A number of blood examinations were made and finally distinct poikilocytosis was recognized, but no nucleated reds were found. A study of the leucocytes at one time showed 9,800 to the cubic millimeter; mononuclears 36½ per cent., polynuclears 55 per cent., and eosinophiles 8½ per cent. The spleen now became enlarged.

Fowler's solution in small doses was given at intervals for a year or more, and rest and freedom from care were advised. Improvement began, and at present the patient reports himself perfectly well. I have not had an opportunity to make a blood examination in the past three years. The last examination of the blood showed no poikilocytes, and the color index was normal; at the same time the spleen was normal in size. I shall not be surprised to see this patient in the near future with the typical symptoms and signs of pernicious anemia.

It is not difficult to recognize the early symptoms of pernicious anemia when once the characteristic blood changes are present. Every symptom seems to take its natural place, and the wonder is that it was not recognized earlier, or that it could be confounded with any other condition. Unfortunately, of my fourteen cases having early gastrointestinal symptoms, in but two am I able to say positively the symptoms appeared long be-

fore the blood warranted a diagnosis. Of the six having early nervous symptoms, in only one case did they appear before the signs in the blood were found, and of the five having early cardiovascular symptoms in only one—the case reported—did I properly interpret the symptoms before the blood showed any suspicious changes.

These four cases were seen early in the disease. In considering the histories of the fifteen cases in which one or more of the symptom groups, which I have mentioned appeared early, it seems to me if it had been possible to study the blood from the first it would have been found, as I positively found in the four cases, that in all, certain premonitory symptoms antedated for a longer or shorter time the appearance of the characteristic blood signs.

I am unable at present to describe a symptom-complex built on the groups of premonitory symptoms I have described in this paper which can be relied on to make an earlier positive diagnosis than can be made from the blood, but I believe a more careful study of these patients in the earlier stages of the disease will give considerable evidence that such a symptom-complex is possible.

In conclusion, I wish to summarize briefly the twenty cases on which this paper is based: They occurred among about 7,300 patients seen in a general medical and consulting practice. The average age was 55 years, the youngest being 27 years and the oldest 80 years. Eleven were males and nine females. All cases had at some time an achylia gastrica. Fourteen had remissions varying from a few months to five or six years. The spleen was enlarged in three cases. Seventeen have died. In only two were autopsies made. The autopsies were noted for the absence of positive lesions. The treatment followed was based on the necessity of rest, fresh air, abundance of nutritious food, a rational consideration of the gastrointestinal symptoms, and the

almost marvelous effect of arsenic. When arsenic could not be taken by the mouth, the hypodermic use was not followed with favorable results. When the gastrointestinal symptoms could not be controlled, the administration of arsenic was useless and even harmful at times.

DISCUSSION.

DR. JAMES B. HERRICK, Chicago, said that in our reliance on the so-called methods of precision and laboratory methods we often overlook a method of great importance in diagnosis, a careful study of the subjective symptoms. In not a few cases he felt sure one could at least suspect the existence of pernicious anemia in the early stage from a consideration of some of the subjective symptoms. There is another period in which much difficulty is encountered, that is, when a patient comes to the office at the time of improvement. Relapses and spells of betterment are very characteristic and at such times we may find the blood picture anything but conclusive. But from a study of the subjective symptoms one might get a clew as to the probable diagnosis. Among those symptoms he wished to emphasize the gastrointestinal as of great importance. Among the other symptoms which seem worthy of note and which might come on early is paresthesia, the so-called spinal cord symptom; in not a few instances the patients complain of numbness and tingling in the fingers, even before the attention is called to the appearance of pallor, weakness, etc. There is another symptom noticed, the symptom to which Hunter called attention, the sore mouth and sore tongue. The more one looks for this in cases of pernicious anemia, the more often will it be noted. Therefore, Dr. Herrick believed that while we should not neglect a careful blood examination, we should pay more attention to the paresthesias and other subjective symptoms which might ultimately enable us to establish fairly definitely a symptom-complex of the disease.

DR. W. S. THAYER, Baltimore, insisted that pernicious anemia is much more common than is generally supposed. He emphasized the importance of paying attention to the early nervous signs. Paresthesia is perhaps the earliest symptom complained of. Dr. Thayer gave illustrative cases.

DR. THOMAS F. GOODWIN, Mount Vernon, N. Y., said that he believes that anemias often arise from conditions within the intestinal canal, from some putrefactive changes occurring in the proteid elements. There being a strong affinity for oxygen, the proteid element undergoes a putrefactive change from incomplete oxidation; this undigested proteid is taken into the blood and gives a good culture media for micro-organisms. This partial oxidation of proteids causes a catabolism from the destruction of nucleo-albumins. If this be admitted, it will

be understood that the changes that occur from the loss of hemoglobin and of nerve nutrition give rise to the symptoms which follow.

DR. G. W. MCCASKEY, Fort Wayne, Ind., said that he believes it to be a reasonable assumption that pernicious anemia is due to some toxic condition; all are practically agreed on this. Whether the toxin or toxins arise from the gastrointestinal tract in most instances, as claimed by the essayist, is open to doubt, but that they are often due to changes within the gastrointestinal tract is probably true. But toxins may arise from various other sources and among them metabolic changes of an undeterminable character. Certain vague symptoms may be found in the preliminary stage of pernicious anemia prior to the development of the characteristic blood changes. These symptoms will be sufficient to enable one to base a suspicion of pernicious anemia, but it appears to be doubtful if they can do more. He thought this was practically the position taken by the reader of the paper himself, who insisted on a careful study of the cases, with vague general disturbances of nutrition indicated by certain nervous symptoms, gastrointestinal disturbances and various other symptoms of a general character.

Dr. McCaskey said that one point is worthy of more attention than it is receiving, *i. e.*, the estimation of the quantity or iron excreeted. If pernicious anemia is due to a hemolytic toxin in the blood, acting on the red cells, there must be destruction of the red blood corpuscles, and the iron in the blood must be eliminated by the kidneys; although some of it might be stored up in the liver or elsewhere. He believes that if examination of these cases during the periods in which the anemia is progressive, would frequently show an increase in the iron excreted. Theoretically, anemia may be the result either of hemolytic toxins or interference with or impairment of the hematogenic function. A distinction may often be made between these two groups of cases if, during the different stages, careful estimations of the quantity of iron excreted are made.

DR. MAX EINHORN, New York, spoke of the invalid to whom Dr. Lichty referred, who suffered from diarrhea, severe anorexia and loss of flesh. She could not go about. She was pale and had a type of simple anemia. The test meal showed achylia gastrica and Dr. Einhorn suggested a diet of eggs, milk, gruel, etc. She changed in ten days and the diet was kept up. Something was given to check the diarrhea. She improved so much that she could go about, and gained 20 or 30 pounds. Three years later the anemia was not so pronounced. Although somewhat pale, she felt practically well. But the gastric contents presented no change. Dr. Einhorn said that he often meets with such cases, in which there is an absence of gastric secretion and a severe type of anemia not pernicious anemia. These patients, if left to themselves with

restricted diet, will die in two or three years, but if treated and nourished well, in nine cases out of ten these patients become active members of society. Some will pick up, but not become entirely well; the appetite does not return, anemia develops, and then an examination of the blood reveals a type of pernicious anemia. He was not willing to say that it is an entirely different disease. He said that he does not know to what condition pernicious anemia is due; but he does know that the condition of inanition, malnutrition of the body, the body being in a bad state, below par, badly nourished, plays a part in the production of a stage of pernicious anemia.

DR. HOWARD S. ANDERS, Philadelphia, called attention to one feature of etiologic value, floating kidney. He had two cases under his care. A woman, 47 years of age, had a moderate degree of pernicious anemia and gave a clear history of gastrointestinal symptoms preceded by traumatism producing a floating kidney. The gastrointestinal disturbance set up by the renal displacement persisted for one and a half years, and resulted apparently in pernicious anemia. This case suggests that correction of floating kidney may help the pernicious anemia tendency.

DR. N. S. DAVIS, Chicago, remarked that all present knew that cord degenerations occur with great frequency in pernicious anemia, but that all do not appreciate that this degeneration is one of the earliest symptoms. This has been impressed on him during the last two or three years, when he met with cases of combined degeneration of the posterior and lateral tracts. In such cases of combined cord degeneration, in which the anemia was slight and was characteristically pernicious, but became so later, anemia should be thought of as a possibility. Pernicious anemia should be kept in mind and the cases watched, because frequently after a time the characteristic symptoms develop. He had in mind several such cases.

DR. C. F. HOOVER, Cleveland, expressed surprise over the statement regarding the early appearance of spinal cord degenerations in cases of pernicious anemia, because he had been in the habit of considering such an appearance as a bad prognostic sign in any case of grave anemia. It was new to him that recovery ever followed grave spinal cord lesions, and he asked if anyone else had ever seen even a temporary recovery in grave anemias after the development of spinal cord symptoms. Patients die of the spinal cord lesions, but not necessarily of the blood lesions.

DR. FRANK SMITHIES, Ann Arbor, said that he does not think that any symptom-complex in the early stages of pernicious anemia can be considered diagnostic which does not include careful and repeated study of the blood picture. Many classes of cases come to the physician which show disturbances of the

nervous system, the heart, the stomach, etc., which do not have pernicious anemia. Although in the early cases the manifestations on the part of these organs may lead one to suspect the disease, it can not be positively diagnosed without study of the blood. If this is not done patients are apt to be improperly treated for years—although this should not be so, inasmuch as the organs supposed to be involved rarely show typical alterations. For example, the dyspnea, the edema, the heart size in those cases which exhibit cardiac disturbances are rarely typical of true, organic valvular disease. He stated that, in his experience, covering the records of more than 100 cases of pernicious anemia, there are always blood alterations in these cases, even the very earliest. There may be only the presence of oval red cells, an occasional megaloblast, or the variation in the size of the red cells. He considered normoblastic "showers" of graver prognostic value than "showers" of megaloblasts. He cited several recent cases in support of this point. Cases with even the most pronounced increases in the number of megaloblasts usually improve markedly if, during these critical periods, they receive careful nursing, feeding and the medication indicated. In all these cases frequent blood examinations are of the greatest value in guiding treatment and prognosis.

DR. JOHN A. LICHTY, Pittsburg, said that the megaloblastic showers indicate that the end is approaching; he seldom saw a patient improve after them. His experience was in accord with that of Dr. Hoover. He had had patients that, so far as the blood picture was concerned, seemed to be perfectly well, but the attacks grew worse. Movable kidney is an unreliable factor etiologically as he finds it in from 30 per cent. to 40 per cent. of all the cases he sees. He said he was afraid to mention movable kidney as a cause of any condition. He wished to bring out in his paper that if one symptom points to the possibility of pernicious anemia, the blood should be examined, especially if cardiovascular symptoms are present. He spoke of one patient in particular whom he treated after she returned from Egypt. She had been sent to Nauheim because of heart disease. She was sent from Nauheim to Egypt for an after cure, and was told to climb the pyramids. It was found that she had had pernicious anemia for a year. He urged more careful examinations in suspected cases.

DIGESTIVE DISORDERS IN PULMONARY TUBERCULOSIS.

JAMES R. ARNEILL, M.D.
DENVER.

During the past ten years I have been greatly interested in enteroptosis and have been on the lookout for this condition in my patients of all classes. The frequency of this anatomic peculiarity in slender patients, suffering with malnutrition, psycho-neuroses and tuberculosis, is decidedly impressive. Most examinations of tuberculous patients do not include an examination of the abdomen. If one palpates carefully for the kidneys, Stiller's sign, and the contracted colon; tests the succussion sounds in the stomach, or inflates it and the large intestines, he will find in a surprising number of cases evidence of enteroptosis. Woods Hutchison remarks that those people who are unusually tall are apt to develop tuberculosis. To my notion, it isn't a question of tallness alone, but of tallness combined with slenderness. Such people are very frequently enteroptotic and are decidedly prone to suffer with malnutrition, psycho-neuroses and all sorts of functional disorders of the stomach and bowels. They are usually below par and anemic, always ailing and taking tonics, and eternally suffering with digestive complaints and a bizarre collection of nervous disorders. A great many of our tuberculous patients are duplicates of these ill-nourished, anemic, psycho-neurotic, constipated, mucous colitic, dyspeptic, enteroptotic wrecks, except that in addition there are present a few symptoms dependent on

the diseased lung, such as fever, cough and expectoration. The treatment most effective in one is often very useful in the other. This consists essentially of fresh air, absolute rest in some, extremely generous feeding, attention to the skin and bowels, optimistic suggestion, and isolation, modified isolation, or diversion and exercise. In many cases it will be wise to employ medicine, such as increasing doses of tincture of nux vomica up to forty or fifty drops three times daily before meals, iron in the form of Blaud's mass, arsenic, sometimes hydrochloric acid, and at other times alkalies, etc. These patients are often suffering from the effects of starvation. Eliminating one article of food after another, they finally limit themselves to toast and tea or malted milk.

The chemistry of the stomach may be normal, or it may show a hypo- or hyperchlorhydria, or may vary from day to day. The mucous membrane is likely to be hypersensitive; in fact, the entire nervous system is usually oversensitive. There may be diminished motility of the stomach. This class of cases is usually helped by Eddyism or psychotherapy; optimistic suggestion and persuasion should occupy a prominent place in the treatment, to dissipate the various phobias. If need be, analyze the stomach contents in order to assure the patient that she is able to digest a generous diet and that only her fears prevent her doing so. Considerable distress may be present at first, but if she grins and bears it, presently, as a result of improved nutrition, the motor and secretory powers of the digestive organs increase, constipation is relieved, nerve tone improves, the nervous system becomes decidedly less sensitive, the vicious circle is broken up and the invalid gets well. In the consumptive the cure must be prolonged and modified to meet conditions as they arise. Frequently a change of surroundings will accomplish all this.

CASE 1.—An enteroptotic young woman, extremely neurotic, with a small healed lesion in the right apex, and a healed

tuberculous hip, was seen in consultation in the Boulder Sanitarium. She had a markedly prolapsed stomach, suffered with frequent retention of food, complete loss of appetite, and greatly diminished digestive power (achlorhydria). A large quantity of albumin but no casts were found in the urine. There was marked emaciation; she was practically a bed-ridden, nervous wreck. A nurse was in constant attendance. She had been in Boulder for two years. It was deemed wise to send her to the Oakes Home, Denver. As a result of the change and the use of the Rose bandage, she began to improve almost immediately. She became decidedly less nervous, the stomach seldom bothered her, the appetite improved, and she gained twenty pounds in weight, and enjoyed good health. This continued for some months, when she again became psychoneurotic. Beginning to have frequent attacks of digestive disorders, with cough, slight fever, loss of appetite, loss of weight, again she became a nervous wreck as before. It seemed wise to try another change, so she was sent to Colorado Springs. Again, in a few weeks, she showed marvelous improvement; appetite improved, bowels became regular, digestion excellent, cough disappeared, stomach emptied itself, and the patient gained twenty-five pounds in weight, and felt better than she had done in years.

Notwithstanding the remarkable work done along the line of opsonic therapy, our sheet anchor in the cure of tuberculosis must be the nutrition of the patient. Here nutrition is meant to include resisting power and antibacterial power. Gain in weight and increase in adiposity are only a part of nutrition. Rest, exercise and fresh air and change of climate to higher altitudes are all of value because they increase appetite and oxidation. They give the patient the capacity to assimilate large quantities of food, increase his nutrition and thus his resisting power to the disease. Tuberculin is of value only when it increases the antibacterial power of the patients' tissues. It can never take the place of hygienic and digestive measures, but should simply supplement them, if it seems wise to use it. All medication which persistently interferes with appetite, elimination and assimilation, must necessarily do harm. Symptomatic medication is often pernicious. Probably more

harm than good has been done with medicine in the treatment of this disease. However, when used judiciously as a supplement to hygienic measures, untold benefit has resulted.

The treatment of a case should be instituted on broad lines, its object being to get at the underlying causes of the trouble and to improve nutrition. One should hew to these lines with tenacity and vigor, seldom yielding to the siren voice of the innumerable symptoms which are begging for relief.

Because of the vital importance of nutrition in combating the disease it is essential that we get as much good work as possible out of the digestive organs; consequently if digestive disturbances are present they should be corrected. Likewise we should attempt to forestall their development. It is remarkable how seldom in our routine work among consumptives, both in private and sanitarium practice, careful investigation and study of digestive conditions are carried on.

Analyses of stomach contents, study of the motor power, size and position of the stomach, the careful study of the stools following or independent of test diets, have been made chiefly in hospitals by investigators who are doing original research work, not by the practitioner for the purpose of helping him treat his cases. Yet if the careful investigation of digestive conditions is of importance in the average dyspeptic, it is of even more value in the consumptive dyspeptic.

It is remarkable, however, that we do not have more digestive disturbances in this disease, when one considers the combination of over-feeding, under-exercise, fever and the various evidences of toxemia present in the consumptive. But with a high temperature he often consumes and digests, without discomfort, three large meals and several small ones each twenty-four hours.

The average case of indigestion in the consumptive can be successfully treated along symptomatic lines. Bitter tonics, hydrochloric acid and ferments, alka-

lies and antifermentatives are used as the symptoms indicate. Occasionally one will find it of decided advantage to give test meals, analyze them and study the motor power of the stomach and the position of the stomach and bowels. During the past three years and eight months I have analyzed the stomach contents in only thirteen of two hundred and thirty private cases of tuberculosis. It is very seldom, indeed, that I have occasion to practice lavage.

In the majority of cases requiring treatment I have been guided by the symptoms and by the experience of numerous workers in this field. In advanced tuberculosis one habitually prescribes hydrochloric acid and ferments because numerous analyses have shown them to be usually absent or reduced. Occasionally one is absolutely wrong in his guess, learning that what he supposed to be a hypochlorhydria with fermentation was a hyperchlorhydria.

In a general way, my results correspond with those of previous investigations, namely, that in incipient tuberculosis the chemism is about the same as in the average person, either normal or hyper or occasionally hypo.

In cases of moderate advancement there is a tendency to hypochlorhydria, though we may find some cases of hyperchlorhydria.

In advanced cases there is usually diminished or absent hydrochloric acid and pepsin, with diminished motor power.

1. Miss G., incipient case, healed, enteroptotic, psychoneurotic, with hypertrophied rectal valves. Free HCl, 0; total acidity, 33.

2. Mrs. W., slight involvement of long standing, enteroptotic, psychoneurotic, suspected hypochlorhydria, but found free HCl, 32; total acidity, 56.

3. Miss P., incipient and quiescent, enteroptotic, psychoneurotic. Free HCl, 24; total acidity, 50. Greatly helped by Rose bandage.

4. Mr. W., incipient, healed; free HCl, 28; total acidity, 50.

5. Mr. W., advanced, hopeless. Free HCl, 10; total acidity, 20. Diminished motility. This patient had a mass in appendix region.

6. Mrs. R., incipient, healed; enteroptotic and extremely neurotic. Free HCl, 50; total acidity, 200.

7. Mr. F., enteroptotic, moderate severity, relapsed after a number of years. Free HCl, 32; total acidity, 54.

8. Mr. F., incipient, healed, gastroptosis. Free HCl, 42; total acidity, 88.

9. Miss E., moderately advanced. Free HCl, 10; total acidity, 60. Persistent diarrhea; stools showed tubercle bacilli; bandage worn. Died a few months later.

10. Mrs. K., moderately advanced; marked enteroptosis. Free HCl, 20; total acidity, 36.5. Persistent diarrhea and stools showed tubercle bacilli.

11. Mrs. B., incipient. Free HCl, 50; total acidity, 70.

12. Mr. L., healed, incipient; markedly neurotic; probably gastric ulcer. Free HCl, 26; total acidity, 68. Riegel test dinner, free HCl, 20; total acidity, 90.

13. Miss D., healed; markedly enteroptotic and psychoneurotic. At times greatly diminished motor power, and four different analyses showed absence of free HCl and hypopepsia. Greatly relieved by Rose bandage.

Of the thirteen patients whose stomach contents were analyzed one or more times, nine had incipient or arrested tuberculosis. Of these seven showed a hyperchlorhydria and two showed an achlorhydria. One moderately advanced case showed normal findings and one a hyperchlorhydria. Two advanced cases showed a hypochlorhydria.

The fact that the motor power is often diminished in advanced cases and in some incipient ones is an argument against giving frequent large meals to these particular patients. The stomach must have an opportunity to empty itself and to rest.

I have found the application of adhesive plaster bandages, according to the methods of Rose or Rosewater, at times extremely useful in enteroptotic cases, with diminished motor power and associated constipation or diarrhea. Patients, however, tire of wearing the adhesive bandages; frequently they can be discarded fol-

lowing improvement or recovery. In case such a support is needed for many months or years Glenard's La-Nea corset belt will be found very useful and convenient.

The following case illustrates the importance of a careful stool examination in diarrheas of tuberculous patients:

Subsequent to marked improvement in a closed sanitarium a patient developed serious gastrointestinal symptoms. There was loss of appetite and persistent diarrhea, with blood and mucus in the stools. The patient had passed from my hands long before this and his physicians made a tentative diagnosis of tuberculous enteritis. Cachexia and malnutrition developed, and the lung lesions became active. The case looked hopeless. By accident the patient discovered the segments of a tapeworm in his stool. Following treatment the parasite was expelled *in toto*; all untoward symptoms speedily disappeared and in a few months the patient more than regained all lost ground, and now is in excellent condition.

Occasionally our tuberculous patients must be operated on for appendicitis, cholecystitis and pyloric obstruction with dilated stomach. Such timely surgical intervention may be the means of turning the tide toward eventful recovery. If time permitted, illustrative cases could be cited.

The dangers of forced feeding are overemphasized by many. That there are real dangers, however, can not be denied.

The production of indigestion and bilious or autointoxication attacks is a frequent sequel. Pathologic obesity occasionally results. Both conditions are fraught with risks for the consumptive. The dangers of indigestion are apparent, as with a single attack the patients may retrograde much in pounds and general nutrition and a quiescent lesion may as a result be stirred into activity.

The dangers of obesity are not so evident, as with many it is thought to be the end and aim of treatment.

The motto of the physician should be to persevere in hyperalimentation till the nutrition has reached an eminently satisfactory point—at the same time guarding

against the production of indigestion and pathologic obesity, with its attendant fatty heart and diminished functional capacity.

Bona fide opsonic therapy is possible for an extremely small per cent. of the vast army of consumptives, but tuberculin therapy—controlled by clinical standards and not by the tuberculo-opsonic index—is possible for a large per cent. of cases, and may prove a wonderful boon to the poor.

Let us have early diagnosis (a very rare thing) and then our simple methods of rest, controlled exercise, fresh air and generous diet will prove successful for most patients, to whom these measures are possible.

In the language of Bruce: "Do not sacrifice nutrition for the temporary advantage of relief from distress."

"The successful treatment of tuberculosis chiefly depends on intelligent guidance of spontaneous resistance and recovery."

DISCUSSION.

DR. WOODS HUTCHINSON, New York, said that this paper emphasized the very important point that there is infinitely more in pulmonary tuberculosis than can be discovered by the stethoscope. In his experience, while a precise diagnosis depends on what is discovered in the chest, the most important information as to prognosis comes from outside the lungs, in the heart and in the abdomen. He believes that too much reliance is placed on the tubercle bacilli for diagnosis. By the time it is discovered in some cases, we may have a post-mortem and make sure of our diagnosis. There are conditions to be detected in the heart and abdomen to aid. In the majority of cases one will find an undersized heart and a tendency to enteroptosis and gastroptosis, gastric dilatation and distension of the colon. Dr. Hutchinson thinks that one of the virtues of the overfeeding treatment lies in the mechanical effect on the bowels of the large amount of nutriment introduced. A patient who has been constipated for months will practically have his bowels regulated merely by the mass of material placed in the stomach which passes to the bowel. Dr. Arneill quoted one of Dr. Hutchinson's statements that tall individuals are more susceptible to tuberculosis, a thing that has been proved. The British Life Guards are recruited, to serve as household troops, from men in all regiments who are over six feet in height. Like all giants, they are not what they are cracked up to be. The artillery,

on the other hand, is recruited from the shortest men, half an inch below the standard of height required by the rest of the army. The death rate among the giants is just double that of the artillery men. These overgrown individuals use too much of their strength in the process of growing.

DR. JUDSON DALAND, Philadelphia, said that all agree as to the importance of a close study of the relation of the gastrointestinal canal to tuberculosis. In regard to the diagnosis of enteroptosis and gastroptosis, he believed the *x*-ray is of use in diagnosing not only the extent of the dislocation or displacement, but also whether the abdominal supporter is accomplishing the purpose for which it was designed, by comparing a radiograph taken before with one taken after the supporter is in place. Another point of great importance in the treatment of such cases is the use of the graded systematic course of exercises done to improve and strengthen the abdominal muscles.

DR. MILTON J. LICHTY, Cleveland, regretted that no statistics were given regarding the frequency of gastrointestinal disturbances in tuberculosis, as well as the frequency of tuberculosis complicating gastrointestinal diseases. From 5 per cent. to 10 per cent. of the patients seen in his office presenting symptoms of indigestion are affected with tuberculosis. One can easily see that there is a relation between the two diseases. He is reminded that tuberculosis has very early symptoms of gastrointestinal disturbances, and one may safely say that gastrointestinal disturbances are a cause of tuberculosis. Those physicians who have the opportunity of seeing a number of these cases in sanatoria could get valuable figures of this condition if they would resort to the use of the stomach tube in a routine way. With patients in the first degree of tuberculosis this procedure should be carried out whenever posible, though he would not recommend it in the last stages of tuberculosis. Such statistics might be of value when carefully compiled. In his own experience he finds that there is about the same proportion of acidities, hypoacidity and hyperacidity in tuberculosis as in any other class of associated diseases. In order to feed tuberculous patients properly, he believed it necessary for the physician to know the condition of the secretion of the gastric juice. He recalled the condition of a patient, tall and slender, who came to him with symptoms of hyperchlorydria, apparently well. When the patient developed tuberculosis later, feeding was comparatively easy. The same is true in hypochlorhydria. He had had several patients whom he treated for a marked hypoacidity for some years. They had malnutrition and they developed tuberculosis while under his observation, possibly on account of the feeding, which in those cases was rather difficult.

DR. J. A. WITHERSPOON, Nashville, Tenn., said that a diagnosis depends largely on the findings in the chest. He finds great difficulty in feeding these patients, especially if they have hypochlorhydria; in such cases the prognosis is invariably graver than when they have hyperchlorhydria. In tuberculosis Dr. Witherspoon has for years been in the habit of first making an analysis of the stomach contents as an aid in the treatment, the object being to know how to feed the patients. Much depends on the nutrition and the patient's power to improve that nutrition. If one has a patient who day after day shows a deficiency in the hydrochloric acid, and deficient motor activity, the prognosis will be worse than if the opposite condition prevails.

DR. JAMES RAE ARNEILL, Denver, said that phthisio-therapists residing at low altitudes deny the specific value of high altitude in the treatment of this disease, maintaining that equally good results can be obtained at low altitude. Physicians living in moderately high altitudes are equally positive that the tuberculous patient does better at moderately high altitudes, other things being equal. Both classes of physicians are influenced by empiricism and clinical experience, not by exact scientific data. The general practitioner, who refers most of the cases, is in a quandary. Dr. Arneill referred to the work of four German physiologists, who attempted to throw some light on this problem by exact scientific investigations. They ascended the Alps, accompanied by a party of soldiers, on whom scientific observations were made. Laboratory apparatus and various instruments of precision were taken along, thus enabling the scientists to make as accurate experiments in the mountains as at home. Their conclusions were that in high altitudes metabolism, especially during physical exercise, is exaggerated; the laying on of proteid material is favored. The activity of the heart is stimulated, the breathing is strengthened, both of them through the medium of the nervous system operating on the heart, and respiratory mechanism. Blood formation is increased, proved by the fact that the number of embryonic red cells, found in the bone marrow on the mountains, is greatly in excess of that usually at sea level, and that the total amount of hemoglobin in the blood of animals, sojourning or born at high altitudes, is greater to the extent of 20 to 30 per cent. than in similar animals studied on the plains. The skin also is trained to more energetic activity. These scientifically proved facts certainly tend to confirm the views of many well-trained clinicians, that altitude has some specific virtues in the treatment of tuberculosis. Interesting and valuable observations—would be the determination of the tuberculo-opsonic indices of patients—before and after sojourning in moderately high altitudes.

SLOW FEVER.

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Synonyms: Typho-malarial fever; simple continued fever; remittent malaria fever; Willacoochee fever; continued fever; bilious fever; typhoid fever.

Definition: A continued fever occurring almost exclusively during the warm months and lasting from one to ten weeks.

From the above list of names, by which this disease has at times been designated, it will be seen that there has been in the past most divergent views as to its causation and real nature. Many physicians living in the swampy regions of southern Georgia maintain that this affection is but a severe form of malaria, while others of equal capacity and intelligence are quite as positive that it is a mild form of typhoid fever; there are not wanting still others equally as capable who hold that the malady is neither one nor the other, but is a separate and distinct disease. These varying views have been maintained by their several advocates probably since the settlement of the country, but proof of their truth has been, so far as I am aware, based only on the clinical aspects that the disease presents and, more recently, on blood examinations for the malaria parasite.

The subject is then seen to be at present in a hopelessly confused state; there was no possibility of an agreement being reached except by actual proof of the truth of one of these opinions by the demonstration of the causation of the disease in question. With this object in view the present investigation was undertaken.

METHOD OF OBTAINING DATA.

It is much to be regretted that the assistants who aided me in this investigation comprised such a small working force that it was out of the question to secure full and complete clinical data in the cases of "slow fever" investigated. The material for the work was collected over a wide area embracing the entire southwestern portion of the state. In a number of instances specimens were sent by the physician in charge—the localities from which they were obtained being too inaccessible for any of us to make a personal visit to the patient—and in such cases we necessarily had to depend on data obtained from the medical man in charge; this accounts for the lack of clinical records in several cases.

It was likewise true that in not a few instances the patients were, on account of ignorance, but little disposed to aid us in our work, and it was only with the greatest difficulty under such circumstances that specimens were obtained. Charts were distributed among the physicians with the request that records be made of the clinical course of the disease in their several patients, but as in nearly all cases these had to be left in the hands of the patient's family to fill out, practically no records of any value were secured. It should, however, be understood that our prime object was to discover the etiology of the disease, and I consequently felt that everything else should be sacrificed in order to determine this; it is gratifying to say that this object has been accomplished according to accepted bacteriologic standards.

ETIOLOGY.

Opinion as to whether or not we have succeeded in ascertaining the etiology of this disease will depend entirely on our views as to the accepted ideas concerning the causation of typhoid and paratyphoid fevers. As is well known, the etiologic relationship of the typhoid bacillus to typhoid fever has never been put to the crucial test of human experimentation, and as typhoid

fever does not occur in the lower animals, final proof of this connection is as yet wanting. This is equally true of the so-called paratyphoid bacillus. Notwithstanding this lack of final proof, a vast majority of bacteriologists agree that these organisms really stand in a causative relationship to typhoid and paratyphoid fever respectively. If this view be correct there can be no doubt of the success of our labors, and although the organisms in question were found in only 73.3 per cent. of all cases investigated, it seems in the highest degree probable that if these germs in reality produce the disease in question more careful and thorough examinations would have demonstrated their presence in all of the other instances.

At all events the typhoid and paratyphoid organisms were isolated in practically three-fourths of the cases under investigation, and agreeably to current views there could be no further doubt as to the real nature of the fever in those instances in which the organisms were found. It is certainly true, whatever views we may hold, that the isolation of these germs in such a large percentage of cases is extremely interesting and more or less significant.

As has been stated, typhoid and paratyphoid bacilli were demonstrated in 73.3 per cent. of all cases investigated; of these the typhoid organism was found in 51.1 per cent., the paratyphoid in 20 per cent. and a mixed infection in 2.2 per cent. of the cases.

CULTURAL DIFFERENTIATION.

As is well known, the isolation of the typhoid and paratyphoid bacilli, particularly from the feces, is a matter of great difficulty. Unfortunately there is a most close relationship between these bacteria and the colon bacillus, so close that it seems to me there can be no question that they are varieties of one and the same organism. Morphologically, and in their staining reactions, it is impossible to distinguish these bacteria one

from another, and it is only by careful cultural experiments that this can be accomplished. This close resemblance had led to a vast deal of work with the idea of devising some method or methods by which it would be possible always to differentiate these bacteria. Thus earlier investigators laid great stress on the fact that the typhoid bacillus usually grows in a colorless film on potato, while the colon bacillus produces a thick grayish pellicle. Much also was made of the fact that as a rule the colon bacillus produces indol while the other organism does not.

A striking peculiarity of the colon bacillus is the fact that it produces gas in media containing sugars, a peculiarity which it does not share with the typhoid bacillus. For a time considerable stress was laid on the fact that in media containing iodid of potassium the colon bacillus usually develops much more rapidly than does the typhoid, but recently this method of differentiation has not been so much employed. Among the further peculiarities of these organisms on which investigators have relied to differentiate them are the facts that the typhoid is usually somewhat more slender than the colon bacillus, that their flagellæ are generally more numerous, that they produce less acid and that their growth is usually not so rapid as is the case with the other organism; the colon bacillus coagulates milk in which it grows, but the typhoid bacillus does not. Unfortunately it has been shown that these various methods for differentiation of the organisms in question can not be entirely relied on, as it now and then occurs that the colon bacillus will show some of the peculiarities of the typhoid organism, and, conversely, the latter germ not infrequently exhibits characteristics that are supposed to be peculiar to the other.

Within recent years highly successful attempts have been made along the line of preparing special culture media, the object of which was to isolate these bacteria from each other by means of the chemical substances

that they produce. Chief among these is the culture medium invented by Drigalski and Conradi[1] and based on the well-known fact that in the presence of both carbohydrates and nitrogenous substances the colon bacillus produces acids from the former, while the typhoid bacillus breaks the albuminous material into products that give an alkaline reaction. This medium contains crystal violet, which is supposed to hinder the development of other bacteria that might be present in the material under examination.

THE MODIFIED DRIGALSKI-CONRADI MEDIUM.

The Drigalski-Conradi medium, when made according to the directions of the originators, was found to give somewhat inconstant results. Following the suggestions of Terburgh,[2] the method of preparing this medium was modified as follows:

2 liters of bouillon (3 pounds of beef to 2 quarts of water).
20 gm. (1 per cent.) peptone siccum (Witte).
20 gm. (1 per cent.) neutrose.
10 gm. (0.5 per cent.) salt.
60 gm. (3 per cent.) agar.
30 gm. (1.5 per cent.) lactose c. p.

After the solution in the autoclave is complete the medium is made faintly alkaline to litmus, 4 c.c. of a 10 per cent. soda solution and 20 c.c. aqueous crystal violet (B. Höchst) solution (1 to 1,000) are added, and the whole is sterilized; 36 c.c. of a sterilized solution of litmus, prepared by pouring boiling water over pulverized ordinary commercial litmus, is then added. The alkalinity of this medium should, at the least, be 0.04 per cent. of pure soda.

Typical colon bacilli on account of the large quantity of acid that they produce turn the medium red in the immediate vicinity of the point where the growth occurs; the acids do not diffuse to any considerable degree owing to the great proportion of agar that the medium con-

1. Ueber ein Verfahren zum Nachweise der Typhus Bacillen, Ztschr. f. Hyg., xxxix, 283.
2. Die auf dem v. Drigalski Conradischen Nahragar wachsenden Bacillen, etc., Centrlb. f. Bakt., etc., xl, 2, 258.

tains. The typhoid colonies do not develop so luxuriantly as the colon and they are more transparent; the medium in their immediate neighborhood remains blue. From the foregoing it is seen that where the two organisms in question develop in a characteristic way differentiation between them is extremely simple.

THE ENDO MEDIUM.

Another culture medium which is quite as satisfactory as that of Drigalski-Conradi for the separation of the two organisms in question is that of Endo.[3] Like the former medium, it depends for its value on the production of considerable quantities of acids by the colon bacillus and the detection of the colonies by the change in color produced in the culture medium on which the organism grows. The medium as slightly modified by us is prepared as follows: To 1,000 c.c. of 3 per cent. neutral nutrient agar add 10 gm. (1 per cent.) lactose, 10 c.c. (1 per cent.) of 10 per cent. soda solution. These ingredients are mixed and sterilized; then 50 c.c. of a sterile 1 per cent. watery solution of basic fuchsin is added. Then 25 c.c. of a sterile 10 per cent. sodium sulphite solution is added, the whole well shaken, and the medium at once poured into sterile Petri dishes. When cold it has a faintly pinkish tinge.

The reason that the above modification was devised was on account of the fact that we found that the medium again became red if sterilized after decolorization by the sodium sulphite. The alkalinity of this medium generally is between 0.1 to 0.15 pure soda with litmus paper as an indicator. It is particularly necessary in preparing this medium to give attention to the following details: 1. The lactose should be pure; if adulterated with cane sugar the typhoid bacillus also produces acids which render its differentiation from the colon bacillus very difficult. 2. The sodium sulphite solution

3. Ueber ein Verfahren zum Nachweise der Typhus Bacillen, Centrbl. f. Bakt. Orig., xxxv, 109.

must either be kept in a well-corked bottle or should be freshly made. 3. The culture medium must be preserved in the dark, as light causes it gradually to turn red. When colon bacilli are planted on this medium the colonies grow rapidly and become very red; a metallic luster quickly appears over their surfaces, which is highly characteristic. The typhoid colonies are small, have a transparent appearance and show only a faint pinkish color.

THE METHOD OF LENTZ AND TIETZ.

In 1903 Lentz and Tietz[4] discovered the fact that malachite green, when added to the customary culture medium, possesses the important property of more or less hindering the development of the colon bacillus, while the typhoid organism is relatively unaffected; this property of malachite green is particularly important where investigations of the feces are being carried on. We were not particularly successful with this method, however, and, as the same object could be attained more satisfactorily in other ways, we did not continue the use of the medium throughout the course of our investigations. It seemed to us by no means so certain as the method of Ficker and Hoffmann,[5] in which the growth of the colon bacillus is hindered by the presence of caffein in the medium; this method is certainly very serviceable, and we believe more reliable than the one just referred to.

GAEHTGENS' METHOD.

Perhaps the best of all the media for the detection of typhoid bacilli in badly contaminated material, such as feces, is the method of Gaehtgens,[6] which is a combination of the procedures devised by Endo, and Ficker

4. Eine Anreicherungsmethode f. Typhus u. Paratyphus Bacillen, Muench. med. Wochschr., 1903, 49.
5. Ueber neue Methoden des Nachweises v. Typhus Bacillen, Hyg. Rundschau, 1904, xiv.
6. Ueber die Erhohung der Leistungsfahigkeit des Endoschen Fuchsinagars durch den Zusatz von Koffein, Centrbl. f. Bakt., etc., xxxix, 5, 634.

and Hoffmann. In this method caffein in the Endo medium hinders the development of the colon bacilli, while the color reactions differentiate these organisms from the typhoid and paratyphoid bacilli. The medium is prepared by simply adding 0.33 caffein to the Endo agar solution already referred to.

It might be mentioned at this point that we have used with entire satisfaction the bent glass rods recommended by Drigalski-Conradi[1] for planting on plates the organisms under investigation. These consist of ordinary glass rods about 20 cm. in length and an arm about 3 cm. long bent at right angles to it at one end. The material to be examined is rubbed up well with water in a sterilized mortar. The culture is then made by inserting the small arm of the glass rod in the mixture, removing with a shake the excess of liquid adhering to it, and then drawing it lightly over the surface of the medium in the Petri dish.

BLOOD CULTURES BY CONRADI'S METHOD.

When it is wished to make cultures from the blood the method recommended by Conradi[7] is undoubtedly of great value—supplanting, in my opinion, the earlier procedures of Schottmueller,[8] who first called attention to the value of bacteriologic examinations of the blood in the diagnosis of typhoid fever. This procedure is based on the fact that the bile has a decided action in preventing the coagulation of blood, while the bacilli grow excellently in a mixture of these two substances. The method is carried out as follows: To ox bile 10 per cent. each of peptone and glycerin is added, and after sterilization 10 c.c. of the solution is meas-

7. Ueber Zuechtung von Typhus Bazillen aus dem Blut mittels der Gallenkultur, Muench. med. Wochschr., 1906, 34, s. 1654.

8. Schottmueller Ueber eine das Bild des Typhus bietende Erkrankung hervorgerufen durch Typhus ahnliche Bacillen, Deutsch. med. Wochschr., 1900, xxxii, 511. Also, Weitere Mittheilungen ueber nehrere das bild des Typhus bietende Krankheitsfaelle hervorgerufen durch Typhus ahnliche Bacillen, Ztschr. f. Hyg., 1901, xxxvi, 368. Zur Pathognese des Typhus abdominales, Muench. med. Wochschr., 1902, xxxviii, 1561.

ured off in as many tubes as may be desirable. Blood is then obtained from the patient by withdrawing it from a vein with a syringe, or, as Conradi prefers, from the ear; 0.5 to 2 c.c. is sufficient. The blood is added to the bile solution and put in the incubator for about sixteen hours. If typhoid bacilli be present their number greatly increases. Cultures are made from this mixture on any of the media by means of which it is possible to determine the true characteristic of any growth that may be present.

In the first instance, then, where it is desired to isolate typhoid or paratyphoid bacilli, I would recommend that in the case of the feces either the method of Gaehtgens or Drigalski-Conradi be employed; in dealing with urine either of these methods or the Endo process may be advantageously used; finally to examine the blood a preliminary culture in the Conradi bile medium may be made, and then subsequently either of the organisms in question may be identified in case they are present.

One of the most satisfactory methods for differentiating between the colon bacilli and the typhoid and paratyphoid organisms is the modification of Rothberger's[9] neutral red procedure devised by Scheffler.[10] The medium is prepared by adding 0.3 per cent. of grape sugar and 1 c.c. of a concentrated watery solution of neutral red to 100 c.c. of nutrient agar. The medium is sterilized and put in tubes and stab cultures made in the usual way. In from twenty-four to forty-eight hours the medium which before was of a dark cherry red becomes partially decolorized and assumes a characteristic greenish fluorescence if colon bacilli be present; there are also numerous bubbles in the medium produced by the liberation of gases from the sugar which it contains. Exactly similar changes are produced by both types of

9. Differential diagnostiche. Untersuchungen mit gefaerbten. Naehrboden, Centrbl. f. Bakt., etc., xxiv, 513; xxv, 15, 69.

10. Das Neutralrot des Hilfsmittel zur Diagnose des Bacterium coli, Centrbl. f. Bakt., etc., xxviii, 199.

the paratyphoid organisms. The typhoid bacillus grows in this medium, but neither decolorizes it nor produces gas.

OTHER METHODS OF DIFFERENTIATION.

Among the other methods that have been devised for the purpose of differentiating colon from typhoid bacilli after isolation may be mentioned the following as of most importance: Escherich[11] first called attention to the fact that the colon bacillus coagulates milk—a property which it does not share with either the typhoid or paratyphoid organisms. Another important differential test was that devised by Chantemesse and Widal,[12] who showed that the colon bacillus ferments lactose, with the production of gas, while the typhoid bacillus does not do this. Schottmueller's paratyphoid bacillus A resembles in this particular the typhoid organisms, while the type B, like the colon bacillus, disengages gas. Petruschky's[13] litmus whey is likewise very serviceable in separating the colon from the typhoid bacillus, the former organism producing acid and changing the color of the medium red.

A modification of the last two tests devised by Wurtz[14] is convenient; it is based on the fact that no gas or reddening of the medium occurs when the typhoid bacillus grows in litmus-lactose-agar, while both of these results occur during the development of the colon bacillus. Paratyphoid bacillus B produces more or less gas in this media. As has been long known, the formation of indol in albuminous media is highly characteristic of the colon bacillus, while this substance does not result from the growth of the typhoid organism; the paratyphoid in this respect resembles the typhoid bacillus. Erdmann

11. Beitr. zur Kentniss der Darmbacterian, Muench. med. Wochschr., 1886, i, 43.

12. Recherches sur le bacille typhique et l'etiologie de la fievre typhoide, Arch. de phys. normal et patholog., 1887, ix, 217, 300.

13. Bakterio chemische Untersuchungen, Centrbl. f. Bakt., 1889, vi, 625, 657.

14. Note sur deux caracteres differentiels entre le bacille d'Eberth et le bacterium coli commune, Arch. de med. exper. et d'anat. path., 1892, iv, 85, 383.

and Winternitz[15] have shown that proteinchrom is produced by the typhoid bacillus in media containing albumins, but this substance does not result from the growth of the colon organism. Just one-half of the paratyphoid bacilli isolated by us produced this substance.

From the foregoing one inexperienced would certainly be led to the conclusion that the differentiation of typhoid from colon bacilli was comparatively an easy matter, but, multiply our tests as we will, there is unfortunately no absolutely certain method by means of which this result can always be accomplished.

PATHOLOGIC ANATOMY.

It is greatly to be regretted that no opportunity permitted the postmortem study of the bodies of those dying of "slow fever," and I am, therefore, not in a position to speak as regards this most important matter. I can only call attention to the fact that in a considerable proportion of cases the spleen was obviously enlarged and that in some instances the lymph nodes were increased in size. In a few cases rose spots were present. These facts certainly tend toward the assumption that this so-called "slow fever" is certainly, in many instances, typhoid, with its well-known pathologic anatomy.

SYMPTOMATOLOGY.

As the primary object of this investigation was, if possible, to determine the etiology of "slow fever," no systematic attempt was made to study the symptomatology of the disease. It was, however, necessary to go into the clinical side of the matter sufficiently to determine that the cases under investigation were true examples of the affection in question. It is not pretended that the symptoms hereinafter enumerated furnish an accurate and clear picture of the malady throughout its course,

15. Ueber, das Proteinchrom eine klinische u. bakteriologisch bisher nicht verwertete Farbenreaction, Muench. med. Wochschr., 1903, xxiii.

but is believed that the principal and most striking clinical phenomena are given. Of the forty-five cases studied records were not obtained in all instances concerning the clinical details; this accounts for discrepancies that otherwise might be puzzling.

In 13 cases the onset of the disease was in April, 11 in June, 18 in July and 2 in September; 36 of the patients were white and 8 were negroes; 23 were males and 21 females; 44 were Americans, and 1 a German; 4 were under ten years of age, 12 from ten to twenty, 13 from twenty to thirty, 5 from thirty to forty, 2 from forty to fifty, and 2 from fifty to sixty years of age; 11 were farmers, 10 school children, 6 laborers, 6 housewives, 3 children, 2 school teachers, 1 a cook, 1 a travelling man and 1 a bookkeeper.

Five of these patients had previously had "slow fever," 3 typhoid, 10 malaria, and 20 declared that they had previously had no fever of any kind. In 12 instances the disease was ushered in by a chill. Headache was observed in 37 cases, and pain in the limbs and back in 38 in the earlier stages of the disease. The appetite was good in 14 cases, and poor in 27. Constipation was present in 18, and diarrhea in 10; in 12 the bowels were regular. Distension of the abdomen and tenderness in the right iliac fossa was present in 17 cases. Nosebleed occurred 6 times.

The fever had varied up to the time of observation from 99.2 F. to 106.6 F. The temperature seemed as a rule to be decidedly higher in the earlier stages of the disease than is the case in typhoid. It did not appear to rise in the beginning and recede at the end in the gradual manner so characteristic of the classical form of the latter disease. The fever was in most instances continual, but showed regular remissions at some time during the twenty-four hours. In six cases intermissions were observed, these usually being present either in the beginning or toward the end of the attack. Rose spots were found in 7 cases. In 20 instances nervous symptoms were more or less pronounced. The heart, and curiously the lungs, also appeared to be normal in every case examined. The spleen was enlarged in 24 cases, and there was more or less general swelling of the lmyph nodes in 23 instances. The liver appeared to be somewhat enlarged in 11 cases.

Stained preparations of the blood by the Romanowski method were made in every instance, and not in a single case was the malarial parasite found. In 18 instances the hemoglobin was estimated; the figures ranged from 60 to 100 per

cent.; the amount of hemoglobin was not entirely dependent on the stage of the disease, as it was found to be very low in several cases during the first week of the disease.

In only 1 case were the leucocytes counted, the number being 7,800 to the cubic millimeter. The average of differential counts in 11 cases is as follows: Small lymphocytes, 17.7 per cent.; large lymphocytes, 9.4 per cent.; polymorphonuclear, 71.6 per cent.; eosinophiles, 1.3 per cent. Agglutination tests were positive in only 12 cases.

In 1 case the malady was complicated by a phlebitis in the leg, and in another deafness and nervous symptoms followed the disease. Death occurred in 2 cases.

It is noteworthy that so far as could be judged from our investigations—irrespective of the bacteriologic findings—the cases studied were essentially alike from the clinical standpoint. The instances in which paratyphoid bacilli were isolated appeared to be in every way as severe as those in which the typhoid organism was obtained; indeed, the percentage of death in the cases studied was even greater, there having been one fatal result out of nine cases of paratyphoid and one out of twenty-three of typhoid.

It is of interest to note that only three of the patients received their water supply from artesian wells, all the others obtaining it from surface sources. In every case but one the houses in which the patients lived were unscreened, these being uniformly swarming with flies, and in many instances mosquitoes also were present in great numbers.

PROGNOSIS.

The prognosis in "slow fever" is generally conceded to be better than in typhoid, and I believe there can be no reasonable doubt that this assumption is correct. The fact, in a large measure, furnishes the basis for the commonly-expressed opinion among southern physicians that "slow fever" is a distinct and separate disease. The mortality in our series of cases is certainly lower than is usually observed in typhoid fever, but, of course, from such a small number of instances of the disease no general conclusions could be drawn.

DIAGNOSIS.

The first thought that always arises in the southern physician's mind when he is called to see a case of fever is: Can it be malaria? He does not depend on the microscope for an answer to this question, but promptly administers large doses of quinin. If the patient responds to this treatment he justly regards the affection as being of malarial origin, but if, on the other hand, no effect is produced he will call it typhomalarial, "slow," or typhoid fever, depending on his preconceived ideas as to the real character of the disease we are studying. Practically, then, it may be said that we may include in the category of "slow fever" all of those instances of hyperpyrexia not responding to quinin, for which no anatomic basis can be discovered and which continue from one to ten weeks.

Of course an examination of the blood for the malarial parasite is of much value, but it should not be forgotten that in those regions where this fever is most common the usual type of malaria is the estivoautumnal, in which it is oftentimes a matter of great difficulty to discover the parasite. Unfortunately the Widal test, even when carried out with the paratyphoid organism, is extremely untrustworthy in this type of fever, it being, indeed, so much so that I am not inclined to lay any particular stress on it.

TREATMENT.

I have had no great experience in the treatment of this disease, but I think everything warrants the opinion that it should be looked after just as is typhoid, a view which I believe I share in common with the majority of southern practitioners. It should be mentioned, however, that many excellent physicians employ large doses of quinin throughout the course of the disease, with the belief that its course is thereby shortened.

DISCUSSION.

DR. J. A. WITHERSPOON, Nashville, Tenn., said that Dr. Harris' description of the continued fever of southern Georgia

does not tally with that seen in the sister state. They have not, in a bacterial way, been able to determine its exact nature. They know that clinically it seems neither typhoid nor malaria. The fever does not respond to quinin, and the plasmodium is not found in the blood. It rarely shows a tendency to respond to the Widal reaction; occasionally the motility ceases, but there is certainly no clubbing together. Clinically Dr. Witherspoon drew some marked distinctions. In the first place there is commonly seen in the South a fever called "toxenteric," and this does not begin like typhoid or malaria. The patient may be taken with a chill, but the fever rapidly reaches its height. One condition always present is the very rapid prostration; the patients are weak from the start. The facies is stupid, a lethargic type of expression being present. The patient is fussy, irritable and, at all times, wide awake. The tongue is not that of typhoid or malaria; it is pale, small, not tremulous and is never dry unless made so by bad feeding or medication. The pulse is not slow as it is in the first week of typhoid fever; it is rapid from the start. The abdomen is not tympanitic unless made so by bad treatment; it is scaphoid. There is no tenderness in the right iliac fossa, but here is tenderness more often found in the bowel, usually over the seat of the sigmoid flexure. Diarrhea rarely is present except when caused by medication. Constipation is usually present with hard scybalæ. Again the disease does not seem to be influenced by the season of the year; it appears at all seasons. Nor does one attack prevent another; there is a tendency to repetition of the attacks, and one man had six attacks of the fever. The slightest thing appears to cause a relapse; any slight error in diet will cause it. Bathing or sponging, which is so grateful in typhoid fever, in this disease brings about sharp recurrence of the chilly sensations which are exceedingly uncomfortable to the patient. These patients are constantly hungry. A thing of particular importance is the rapid change in the temperature chart. The temperature may be 105 at 8 o'clock in the morning, 101 or 102 at 10 o'clock, and at dark 101. It is a fluctuating temperature like that of a septic type of fever. There is the cold and clammy skin and profuse sweat. This is the fever that occurs in the South more frequently than any other, either malaria or typical typhoid fever. Whether or not it is an atypical typhoid fever Dr. Witherspoon can not say. None of these patients dies unless treated too much.

Dr. Edward J. Wood, Wilmington, N. C., said that he sees many cases of extremely mild typhoid fever, closely resembling the fever described by Dr. Witherspoon. This fever runs a course of from three to six weeks, often with no diarrhea or tympanites, but there is always a positive Widal reaction. Many times these cases go undiagnosed, and few would ever be considered typhoid were it not for the blessing of an occa-

sional hemorrhage. Often the mildness of the infection is a misfortune, as it is hard to convince the people that it is really typhoid, hence the difficulty in carrying out proper hygienic precautions. This danger of epidemic is enhanced by the lack of any system of sewage, and by the surface well, which supplies the drinking water. This well is usually close to the closet. It is difficult to determine the relation of malaria to the atypical fevers, as the people take quinin so constantly and the organism can not be found in the peripheral blood, as a consequence. It is a good rule that a fever of this type that does not respond to quinin, properly administered, in from five days to a week, may be safely considered typhoid.

DR. JOHN A. LICHTY, Pittsburg, said that since his practice is in Pittsburg, a place that all know has more typhoid fever cases than any other city in the union, he believes that he can speak with some experience. It seemed to him that Dr. Witherspoon pictured cases in the South that he has had, with the same symptoms, and in which was found the Widal reaction, and which he called typhoid fever. One of the greatest stumbling blocks to students leaving the medical schools is that diseases do not run typical courses. In Pittsburg there are these atypical cases of typhoid fever, the same that are found everywhere, cases with rapid pulse, unusual condition of the tongue, and yet physicians do not hesitate to call them typhoid. They do not have malaria in Pittsburg, therefore, these are not malarial.

DR. ALEXANDER LAMBERT, New York, asked if Dr. Harris made blood cultures in that type of fever during the first ten days; it has become a routine measure at Bellevue Hospital to make a blood culture in fevers suspected to be typhoid. The positive blood cultures obtained are surprisingly great, above 90 per cent., especially during the first ten days. The Widal reaction is an excellent aid if positive; if negative at the time it was first being made, diagnosis must depend on other symptoms as it did years ago before the reaction was known. Dr. Lambert believes the blood culture to be an accurate and useful method of diagnosis in doubtful cases, especially during the first ten days.

DR. MILTON H. FUSSELL, Philadelphia, said that the cases reported by Dr. Harris could not be malarial if no malarial organisms are present. Blood cultures will appear positive in at least 73 per cent. of cases of typhoid. He has never practiced in the South, but to say that typhoid fever exists there in various forms is sufficient to make southern practitioners endeavor not to allow the disease to be spread. The term "typho-malarial" is a sheet to cover ignorance and should be abolished. Ninety per cent. of the cases diagnosed as "typho-malaria" in the soldiers in the Spanish-American War were true typhoid fever. To be sure, malaria and typhoid fever may exist in an

individual at the same time, but the term "typho-malarial fever" ought to be excluded.

DR. H. F. HARRIS, Atlanta, Ga., said that he was satisfied that the commonly accepted view is erroneous that this so-called "slow fever" is an exceedingly mild disease. He is equally certain, however, that it is not so severe as is typhoid fever in the northern portion of the country, where he had had an abundant opportunity of observing it in the past. The view that "slow fever" is very rarely fatal arises from a not unnatural tendency of the physician to forget the real facts. Since a hundred cases are seen during the course of perhaps four or six years and as probably not more than five or six patients die, the physician who keeps no records would almost inevitably have a strong tendency to minimize the dangers attending the malady. It is also true that many physicians consider the severe cases terminating in death as typhoid, and consequently these are not reckoned among the cases of "slow fever." Typhoid organisms were isolated from the blood in six of the cases and paratyphoid in one. More frequent success would have been obtained had it not been that the patients were, as a rule, exceedingly ignorant and much opposed to the abstraction of blood in sufficient quantity. Dr. Harris said that, after Conradi's ox bile method was published he was more insistent in the endeavor to obtain blood for diagnostic work, but the ignorant opposition of the patients generally prevented.

THE PHYSIOLOGY OF THE THYROID GLAND IN ITS RELATION TO EXOPHTHALMIC GOITER.*

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The investigations of the last twenty years have given to the thyroid gland a physiologic importance of the first order. So enthusiastic have some observers become in their belief in its primal position in physiology and also, on the part of a few, in therapeutics, that one is almost tempted to compare its supposed potency to the famed fountain of eternal youth whose magic healing and rejuvenating properties was the hope of the aged, infirm explorer. I must confess myself as among those who share the belief that the thyroid is a true gland, whose proper functioning plays such a part in the physiologic rhythm of the body that it stands very near to, if, indeed, not in, the list of viscera to which the term vital is properly applied. I share also in the belief that the thyroid proteids have a wide range of beneficial therapeutic activity, and yet I must, in the beginning of this discussion, call attention to how little scientific knowledge we have of the real significance of the gland and its mode of functioning, and to how large a degree our knowledge is the plainest empiricism.

We know that complete removal of the thyroid apparatus, i. e., thyroid and parathyroid, leads in most species of mammals to a fatal issue in the majority of cases. We may now safely conclude that such a result

* From the Loomis Laboratory, Department of Experimental Pathology of Cornell University Medical College.

is due wholly to the removal of the glands and not to a traumatic injury of the nerves in anatomic proximity to the gland. Death from such a complete operation is generally sudden and follows a varying period of severe tetanic convulsions. I think that as a result of the experimental work of the past ten years we may go further and state that the thyroid apparatus is complex and has two well differentiated histologic structures, thyroid and parathyroid, and we have good reasons for believing that the different histologic structure corresponds to a different function. Removal of the thyroid alone is followed in most cases by a cachexia, which may in large part be relieved by the administration of thyroid substance. Removal of parathyroids, if complete, is followed by an acute fatal tetany which supervenes in a few hours or a few days.

During the last few months I have carried out some further experiments on this line which give additional evidence of their different function. The experiments have in all cases been made on dogs. The acute tetany has been induced by operative removal of the parathyroid glands. While the animal was in severe convulsion, a hypodermic injection of beef parathyroid nucleoproteid has been given with the result that in from thirty minutes to two hours nearly all the animals have temporarily recovered a normal condition. The improved condition does not last, however, for muscular twitchings begin again in from 24 to 60 hours, and the animal rapidly passes into a tetanic condition. Another injection of the parathyroid nucleoproteid a second time will relieve the animal. The whole procedure may be repeated a third time, but we have not thus far succeeded in keeping an animal alive longer than three weeks after such an operation, but we can nearly always prevent death in the acute tetany. We have some evidence that the convulsions following the operation are due to a toxic condition of the blood, for if animals are fasted for a few days or if they are fed on meat-free

diet the convulsions are less severe and appear later than they do if meat is given. Severe convulsions can be brought about in two or three hours by giving an operated animal a heavy feeding of meat. MacCallum's experiments have shown that bleeding the animal in tetany and infusing with normal saline will likewise relieve the convulsions. Further, the blood of an animal in tetany was found to be very toxic to an operated animal before enough time has elapsed for the animal to have tetany from its own operation. The globulin from the parathyroid has thus far failed to relieve the symptom, a fact which indicates a difference in chemistry from the thyroid, as in the latter gland the peculiar iodin group is in combination with the globulin and is, therefore, the proteid of particular physiologic activity.

The older experiments did not differentiate between thyroid and parathyroid, so that the acute tetany following the complete operation has been by them ascribed to the thyroid insufficiency. There are observations on record of relieving the acute symptoms by large doses, 4 to 5 grams, of iodothyrin per day. Such doses are far beyond the limits of the physiologic and are not to be compared to the very small amount of parathyroid-nucleoproteid required to do the same thing.

The observations on the effect of operative removal of the glands and on the administration of various components of the glands to animals operated on and to normal animals constitute the most important known facts about the physiology of these structures. And the facts are briefly as follows:

1. Removal of the thyroid causes cachexia thyreopriva, the symptoms of which may in large part be alleviated by administration of thyroid preparations. Thyroid extracts owe their activity largely to the organic iodin group therein contained.

2. Removal of the parathyroids is followed by an acute tetany. It is on the above observations that all the interesting and suggestive theories useful in the physio-

logic and therapeutic value of the glands have been founded. Some of these theories have sufficient dignity to command serious respect, but in many of them there is a lack of regard for the fundamentals.

It is a well-authenticated fact that thyroid feeding stimulates nitrogenous metabolism, and it may be that such a stimulation is accompanied by a heightened oxydative capacity of the organism by which toxic products of metabolism are rendered harmless. Hunt has recently furnished the first experimental demonstration of the detoxicating action of thyroid by showing that mice fed with thyroid preparations are able to stand larger doses of acetonitrile without fatal effect than control animals. The beneficial effects in these experiments are not to be ascribed to a direct chemical union of thyroid with acetonitrile, but rather through the metabolic stimulation which the gland extract caused. Although the detoxication theory of thyroid function has very little direct experimental evidence to support it, there is some empiric clinical evidence in its favor and it has been used by Moebius as the foundation of his treatment of exophthalmic goiter. The blood of thyroidectomized animals contains a somewhat different distribution of proteids than is found normally, in that there may be an increase in the ratio of globulin and a diminution in the hemoglobin, but there is little experimental ground for supposing that the blood of thyroidectomized sheep contains a toxin, and there is absolutely no reason to believe that this toxin, if it does exist, can combine in quantitative chemical fashion with human thyroid secretion. The supposed mechanism of this therapy is purely hypothetical and is without any analogy in known physiologic action. To Moebius belongs the credit for first formulating our notions of the hypersecretion theory of exophthalmic goiter, but his means of treatment has the most empirical foundation.

A unique detoxication theory of the function of the

thyroid and its rôle in exophthalmic goiter has an ardent supporter in Blum, who believes that there arises in the course of metabolism a toxic globulin which is detoxicated in the thyroid by the chemical addition of rodin. The colloid is, therefore, an excretory product and the more perfectly it is iodized the less toxic effect should it have. (According to this theory exophthalmic goiter is caused by the escape into the circulation of large quantities of this partially iodized proteid.) The theory is based principally on Blum's observation that iodin can be added to the thyreoglobulin *in vitro* with the result that its peculiar physiologic properties are completely lost. The latter observation is probably correct, but granting that it is, no conclusions worth entertaining can be drawn from it. Blum's theory contradicts the experimentally demonstrated facts that the iodized proteid from the glands is responsible for much of their physiologic activity, and the equally well demonstrated fact that the activity is proportional to the iodin contained. If potassium iodid be given to an animal there is an increase in the content of physiologically-combined iodin in the gland. Roos has shown that when the glands from animals fed with large quantities of potassium iodid are tested physiologically they show an activity proportional to their iodin content, whereas, according to Blum's theory, such glands should have less physiologic activity than the normal. The artificial iodizing of a proteid *in vitro* is a violent chemical action not to be compared to the behavior *in vivo*. We know, furthermore, that the beneficial effects of thyroid treatment in myxedema may be produced by the circulation of the organic iodin group, a fact which is directly contrary to Blum's hypothesis. His theory of thyroid function will not bear close inspection, but the cause of the exophthalmic symptoms, by an escape of large amounts of partially iodized globulin into the circulation, is identical with the belief generally held to-day. I am personally inclined to believe that one

function of the gland may be a detoxication, but I do not believe that this is accomplished by a direct chemical union of the thyroid secretion with a metabolic toxin, but rather by the stimulating and regulating effect which is exerted on other viscera.

Chemical studies of the gland have demonstrated the presence of three forms of proteid, nucleoproteid, globulin and albumin, in addition to a number of the simpler cleavage products of proteid, the latter being bodies of no especial significance. The normal thyroid contains relatively little of the nucleoproteid, much globulin and a smaller amount of albumin; the parathyroid, on the other hand, contains a large amount of nucleoproteid, a very small proportion of globulin and still smaller amounts of albumin. These findings agree with what we should expect from the histology, and in each case the proteid present in greatest abundance is the one most active physiologically. Since the discovery and isolation of the organic iodin group by Baumann most of the chemical study of the gland has been directed toward that compound and the proteid of which it forms a part —thyreoglobulin. This is proper from a physiologic point of view, but from the pathology of the gland we must not fail to consider the nucleoproteid. I have had an opportunity during the past two years to separate the nucleoproteid and globulin from a large number of thyroid glands, normal, simple hyperemic, glands with marked cellular hyperplasia, simple adenoma, colloid goiter, and glands from practically all stages of exophthalmic goiter. In most of the glands from the latter condition there has been found a much larger proportion of nucleoproteid, particularly in the fatal cases. The normal conditions may be entirely reversed and the nucleoproteid be found in as great preponderance as the globulin in the normal gland. Additional confirmation of this point is found in the statements of Kocher and Aeschbacher, that when the gland is rich in phosphorus it is poor in iodin. The phosphorus comes chiefly

from the cell nuclei which are much more abundant in the exophthalmic gland. Histologic evidence supports this finding, as in the late stages of exophthalmic goiter there may be found considerable cellular hyperplasia with relatively little colloid. There is practically no experimental evidence on the function of the nucleoproteid as distinct from the globulin, yet in certain pathologic conditions the former must play an important rôle and one of which we are as yet entirely ignorant.

The study of thyreoglobulin and its content of iodin has been the main chemical contribution of recent years, and it is especially to Oswald that we are indebted for much of the work since Baumann's time. Oswald has determined the content of thyreoglobulin and iodin in many normal glands and simple colloid and parenchymatous goiters. He finds in goiter a great variation in the relative and absolute amounts of globulin and iodin, but his findings may be summarized by the statement that in goiter there is a relatively large amount of globulin poor in iodin. Although he has reported only four analyses of these glands, he bases thereon his latest theory of the disease, viz., a flooding of the system with a globulin poor in iodin. Such a theory really means a hypersecretion of a product of less physiologic activity than the normal. If we consider, however, that normally the blood supply is so great as to permit the entire volume of blood in the body to pass through the gland fourteen times in twenty-four hours, and consider also to how great an extent this blood supply is increased in exophthalmic goiter, we must conclude that this theory means simply an excess of effective thyroid secretion in the circulation. Even though there is less iodin in the proteid than normally, there is no evidence that this indicates a change in the essential character of the proteid. There may be less activity per unit of globulin, but since there is such an increase in the number of units in circulation the conclusion of the chemical study is in favor of the hypersecretion theory. Oswald

entirely ignores other proteids than the globulin, a decision which I wish to emphasize again is not satisfactorily explained. The chemical findings in colloid goiter can not be used in an argument on exophthalmic goiter, since in so many cases the nucleoproteids in these latter glands is quite as important a constituent as the globulin. Although the chemical studies indicate that in exophthalmic goiter the globulin contains proportionally less iodin, such a result does not imply a dysthyroidization as a factor in the disease, for the iodin in the proteid is a measure of a quantitative rather than a qualitative change. The clinical argument that the many types of the disease can only be explained by a dysthyroidization may have some support in the fact that nucleoproteid and globulin are found in glands of exophthalmic goiter in different ratios from those in the normal gland, but an equally probable explanation is to be found in the personal idiosyncrasy toward active proteids.

We know very little of what the thyroid secretion does when confined within physiologic limits, but if given in excess we see as a result many of those symptoms characteristic of exophthalmic goiter. The exophthalmos, tachycardia, tremor, gastrointestinal disturbance, profuse sweating, increase in temperature, rapid loss in body weight, severe mental disturbance, have all been caused experimentally in animals by overdosing with thyroid preparations. It has thus far been impossible to produce the disease experimentally, and the nearest approach has been obtained by giving an excess of thyroid extracts. There is, however, a serious error in technic in most of these experiments in that the commercial thyroid has been given in intermittent doses by stomach in most cases, but if the physiologic conditions are to be simulated a saline extract of the gland from the same animal species should be given in small, frequently repeated doses hypodermatically. Even then we are not providing the most suitable conditions, as the extract of a nor-

mal gland has a distribution of proteids somewhat different from those the diseased secretion contains. One of the most interesting experiments of this kind is that reported by Dr. Matthes, who had a patient suffering from exophthalmic goiter operated on with a curative result. Later when the patient was fed portions of his own dried gland there was an increase in the nitrogen execretion with some return of symptoms.

However, granting that, as seems probable, the hypersecretion theory offers the most satisfactory explanation of the origin of the symptoms in the disease, we as yet have no satisfactory explanation of the mechanism by which they are brought about. The tachycardia, for instance, has been variously explained, an acceptable theory to many students being that of Gley, who believes the vagus impulses are inhibited and the accelerator stimulated by the gland extracts; yet very recently some experiments on the isolated heart have indicated that the central nervous system may be in no way concerned in the matter.

The mechanism responsible for the other symptoms of the disease are in a more unsatisfactory condition than the tachycardia. The very rapid loss in weight has been repeatedly given a partial explanation by the stimulating properties which the gland extracts have, but why and how the extracts act in this manner is a subject entirely unknown to us at the present time. The metabolism of patients suffering from exophthalmic goiter has been partially studied in a number of laboratories, and as a result we know that very large amounts of nitrogen are required to maintain an equilibrium during some stages of the disease. Recently in our laboratory more complete analyses of the urine have been made by Dr. Shaffer, and the most interesting new fact which can be drawn from these studies is that the kreatinin excretion is low compared with the normal, and the lower figures always go with the more severe toxic forms of the disease. When the patient improves there is a

corresponding rise in the kreatinin output. With the low kreatinin excretion there is an increased kreatin excretion. We know little of the origin of kreatinin in the body, but Dr. Shaffer has recently advanced the theory that it is a measure of the muscular efficiency; such a theory is supported in this disease by abundant clinical evidence and by the measurements of the strength of selected groups of muscles made by Dr. Frederich Muller, who has found that in patients suffering from exophthalmic goiter the muscles are no more than one-fifth to one-third as strong as in normal individuals.

There are two commonly accepted possibilities which explain the origin of the hyperactivity of the gland. First, as a result of nervous shock; second, as a compensatory hypertrophy during a toxemia.

As to the first possibility, the investigations of the last ten years have given us a fund of information concerning the remarkable control exercised by the nervous system on glandular activity. Particularly with reference to the digestive glands we have seen qualitative and quantitative changes in their activity following an apparently insignificant stimulus. We have no direct experimental evidence to indicate in how far we can apply these results to the thyroid gland, but clinically we see many instances of marked change in the activity of the gland following some profound nervous disturbance. The condition may have been latent before and first becomes evident following some severe fright or sudden sorrow. Why the effect should last beyond the stimulus which called it out we do not know. That a new habit of abnormal activity may result from a series of repeated stimuli is an hypothesis put forward to account for many instances of physiologic overwork, and it may apply here.

As to the second hypothesis, there are some histologic studies which indicate that during the infections and also during chronic toxemias the thyroid undergoes cellular hyperplasia which may serve in the nature of a

compensatory hypertrophy, i. e., the additional demand for the detoxicating action of the gland results in its growth. At present we have no method of measuring the activity which the gland has either in a normal or pathologic condition and can form only the crudest notions by the gross appearance and histologic structure. It is, therefore, rash to conclude that in those cases of exophthalmic goiter with no goiter there is no hyperthyreosis. There are many clinical observations that support the theory of compensatory hypertrophy, and it is the mere bulk of this evidence rather than its character which is impressive.

In conclusion I must again call attention to our dearth of knowledge of the physiology of the thyroid gland and the pressing need for systematic, careful investigation, both on the part of the laboratory worker and the clinician. Theories we must have, for it is by these that we grow, but the danger lies in accepting an attractive theory as an established fact.

THE PATHOLOGY OF EXOPHTHALMIC GOITER.

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The symptom-complex which we know under various names as exophthalmic goiter, Graves' disease, Basedow's disease, etc., has been very extensively studied, but even yet there is not perfect unanimity of opinion as to the anatomic changes which underlie these symptoms. Nearly all writers, except certain clinicians who have not made anatomic investigations, agree that there are always changes in the thyroid, although there has been much debate as to whether these changes are constant in character or not. There are others who think that the lesions must be sought in the sympathetic system or in the central nervous system, while still others regard the disease as the result of a functional disturbance of the nervous system and do not expect to find gross anatomic changes. Other attendant lesions in the eyes, in the skin, the muscles, the digestive tract and in the lymphoid tissue and thymus have been frequently described, and organs of internal secretion other than the thyroid, such as the parathyroids, adrenals, pancreas, hypophysis, etc., have been investigated with varying results. Since Moebius put forward his idea of the fundamental relation of the thyroid to the disease, attention has been centered chiefly on that organ and it has formed the point of attack in therapeutic measures, but the other lesions must still be regarded as worthy of close study, and in this paper the changes found in a rather

large series of cases will be taken up in order. It must be observed, however, that none of the changes which have been generally found and which I have found in my series have the character of primary changes. They seem in each instance to be the response or reaction to some fundamental or primary disturbance of which as yet, I think, we have no very clear notion.

Disturbances of metabolism in these cases are obvious, and these seem to be intimately connected with the fundamental activity and corresponding anatomic condition of the thyroid, but whether as cause or effect is not absolutely proved. Similarly pronounced nervous disturbances occur, the heart runs riot, the body trembles, secretions are disturbed and the mental condition and temperament are altered, but whether this is the result of chemical changes or of obscure anatomic lesions in the nervous system we are not certainly informed. Whatever vague notions we have as to the fundamental underlying cause of all these things we may discuss after describing the anatomic changes.

It has been shown by Halsted and others that if a portion of the thyroid be removed from an animal the remainder shows after some time a curious alteration, which consists essentially in the great proliferation of the epithelial cells by a process of mitosis. So great is this new production of cells that they become too numerous to be accommodated on the smooth wall of the round alveolus and the epithelial lining accordingly becomes folded in the most complicated way, each fold carrying up with it into the original lumen a supporting strand of connective tissue with blood vessels. This change in the alveolar wall is followed by a decrease in the amount of visible colloid, which loses its hyaline dense appearance and becomes pale and ragged. The whole process has been regarded by Dr. Halsted as a compensatory hypertrophy, the proliferation of the epithelium being an attempted repair of the loss of thyroid substance. A similar condition is found in a small per-

centage of stray dogs in Baltimore and occasionally in sheep and goats, while in certain localities, as reported by Dr. Marine, in Cleveland, in a recent paper, an enormous proportion of the stray dogs are thus affected.

What the cause of this hypertrophy can be is not perpectly clear, but Dr. Marine has observed that if these dogs be given iodids in considerable doses the alveoli again become round and filled with colloid, and Dr. Kocher tells me that the administration of iodin will prevent the development of the folded condition after the operative extirpation of part of the thyroid.

Now in exophthalmic goiter the thyroid presents an appearance practically identical with that found in these animals, and it will be my task to describe in greater detail these anatomic appearances as they occur in this disease. It is true that none of the symptoms found in exophthalmic goiter are observed in the animals operated on nor in those in which the hypertrophied condition occurs spontaneously, but still the analogy is of great interest.

The material which I have had for study consists of sixty patients, most of whom have been operated on by Dr. Halsted for the relief of symptoms more or less typically those of exophthalmic goiter, and I am much indebted to Dr. Halsted for this material. Not all of these cases presented the complete typical picture of exophthalmic goiter; some of them, as will be recounted, showed part only of the characteristic symptoms, while some were complicated by the presence of other lesions of the thyroid and other organs. It will be of interest, however, to determine in how far the anatomic changes correspond with the development of symptoms, and this can be done briefly, more exact data being obtainable from the table appended.

From this table it is seen that in certain cases the changes in the thyroid are very well marked and are of a characteristic type, while in others they are less easily recognizable.

TABLE OF EXOPHTHALMIC GOITER CASES.

Case.	Character of symptoms.	Duration.	Character of thyroid.
W.	—Typical	6 mos.	Typical.
R.	—Indefinite		Colloid adenoma, indefinite changes.
H.	—Typical		Typical.
S.	8070.—Typical	3 yrs.	Typical.
C.	8076.—Typical	6 yrs.	Typical combined with adenoma.
H.	2894.—Typical	3 yrs.	Typical.
S.	8074.—Typical	1 yr.	Typical.
M.	8066.—Indefinite, no exoph. no nervousness	2 mos.	Normal.
S.	7142.—Typical	8 mos.	Typical.
B.	7536.—Indefinite	1 yr.	Colloid adenoma, slight hypertrophy of epithelium.
T.	5216.—Indefinite, no exophthalmos.	3½ yrs.	Cyst with wall of hypertrophied thyroid tissue.
D.	5045.—Typical	1 yr.	Typical.
Y.	6886.—Typical	1½ yrs.	Typical.
E.	7425.—Typical		Typical.
H.	7321.—Typical	8 yrs.	Typical.
R.	7278.—Typical	1 yr.	Beginning folding in walls of large alveoli.
C.	7375.—Typical	3 mos.	Typical.
J.	6955.—Typical		Typical.
S.	7351.—Moderate	5 yrs.	Large alveoli, slight folding.
G.	7122.—Typical	2 yrs.	Large alveoli full of colloid, complicated folding.
L.	7897.—Typical	3 mos.	Typical.
F.	—Indef. goiter, nervousness	1 yr.	Beginning changes in walls of large alveoli.
S.	8071.—Indef. tachycardia	18 yrs.	Exoph. changes in adenoma, not elsewhere.
S.	8046.—Indef. exoph. tremor, no goiter.	5 yrs.	Beginning changes in walls of large alveoli.
P.	5883.—Indef. nervousness, tremor, no exoph.	1 yr.	Normal.
G.	6202.—Typical		Typical.
B.	7158.—Indef., no exoph., tremor, wasting.	2 yrs.	Beginning changes in walls of large alveoli.
T.	7212.—Indefinite, tremor only, pulse 100	Gradual	Indefinite, beginning changes.
A. I.	7953.—Typical	6 mos.	Typical.

Case.	Character of symptoms.	Duration.	Character of thyroid.
N. 610.	—Typical	2 yrs.	Typical.
T. 2775.	—Typical	3 yrs.	Typical.
H. 4017.	—Typical	6 mos.	Typical.
H. 4055.	—Typical	2 yrs.	Typical.
R. 4170.	—Typical	2 yrs.	Typical.
C. 4538.	—Typical		Typical.
S. 2079.	—Typical	4 yrs.	Typical.
W. 4808.	—Typical	2 yrs.	Typical.
W. 5254.	—Typical	2 yrs.	Typical.
D. 5334.	—Typical	8½ yrs.	Typical.
B. 5335.	—No exoph. goiter, tremor, tachycardia.	1 yr.	Foci of proliferation, much colloid, lymphoid hyper.
L. 5379.	—Typical	9 mos.	Typical.
M. 5404.	—Typical	3½ yrs.	Typical.
W. 5582.	—No exoph., nervousness, tachycardia, goiter.	1 yr.	Foci of typical change, other areas normal.
S. 5634.	—Indef., goiter with tremor only	1 yr.	Colloid adenoma.
G. 5199.	—Goiter 28 yrs.; exoph. symptoms 5 mos.	5 mos.	Indef. changes in old goiter.
F. 5651.	—Typical	2 yrs.	Much folding in large alveoli; typical.
B. 5806.	—Typical	8 mos.	Typical.
S. 5873.	—Indefinite	8 mos.	Colloid adenoma.
E. 5914.	—Slight symptoms	6 mos.	Slight changes in large alveoli.
M.	—Typical		Typical.
L. 5991.	—Typical	13 mos.	Typical—focal.
E. 6019.	—Typical, moderate	6 mos.	Typical.
W.	—Typical	5 yrs.	Typical.
H. 4744	—Typical	3 yrs.	Typical.
K.	—Typical	2 yrs.	Typical.
P.	—Typical, moderate	5 mos.	Typical.
H.	—Typical	2 yrs.	Typical.
J. 2827.	—Typical	15 yrs.	Typical.

The more characteristic changes may be discussed first. In most instances the thyroid is enlarged, although, as a rule, not to a great size; in some cases it is not larger than the normal or it may be actually decreased in size. At operation the superficial veins are found to be very large and easily torn and are distended with blood so that the gland has a very congested appearance. This is not striking in the excised portion, since the vessels collapse and on section the interior of the gland tissue is rather pale. Usually the tissue is

hard and rather rigid than elastic. Its normal amber red translucence gives way to a grayish opacity and the fresh cut surface, instead of being glairy or gelatinous in appearance, tends to be rather dry and granular. This varies, however, with the amount of colloid material in the alveoli, and in many advanced cases the cut surface may be still moist and give off a little glutinous material. The surface of the gland is usually somewhat nodular and rough, and this is seen to be true also of the surface, in which it is found that fine strands of fibrous tissue traverse the glandular substances, separating it into lobules.

Usually the change is diffuse throughout the whole gland, but sometimes one lobe may be much larger than the other, and in some cases the alterations described are present only in small patches here and there throughout a gland which otherwise seems nearly normal. These foci are easily distinguished by their fine grain and by their opacity from the adjacent colloid holding tissue.

Microscopically there is found the change which appears in the experimental compensatory hypertrophy. Strands of fibrous tissue run in every direction like scars through the gland and separate the tissue into lobular masses, and in these lobules the alveoli are often still separated by a fibrous tissue stroma much more abundant than in the normal gland. The alveoli are no longer rounded, full of colloid, and lined with low cubical epithelium, but are extremely irregular in size and in form. As a rule most of them are smaller than normal, while in the central part of each small lobule there are larger alveoli of very irregular outline, sending out diverticuli in every direction and encroached on by epithelial projections which extend into their lumen. With some special method of staining the connective tissue it may often be made clear that such a small lobule is probably a sort of colony in which the smaller peripheral alveoli are derived from the more centrally placed or are actually merely sections of the diverticula of the central

ramifying alveolus. This alternation of large irregular alveoli with small ones ranged round them is very characteristic and evidently results, in part at least, from the separation of portions of the central cavity in the form of new alveoli.

The epithelium becomes columnar not only in the large alveoli, but in the small ones as well, and thus occupies so much space that there is but little lumen left. Indeed, the areas occupied by the small alveoli may appear almost solid, so small are their cavities and so scant the colloid. In most instances the epithelium is very regular in its form throughout and the details of its structure can be made out very clearly. The cells are plump, with a finely granular protoplasm and a sharp outline. The free surface is very sharply marked and is sometimes slightly dome-shaped. The nucleus may lie near the base or near the free end of the cell. Mitotic figures are frequently to be found. Occasionally some of the cells appear narrow and shrunken and biconcave in form, with a very deeply stained nucleus and dark red protoplasm. These are the so-called colloid cells of Langendorff, thought by him to be especially concerned in the secretion of colloid, but which seem to us rather more like the result of some degenerative process. Only rarely could the so-called *Schmelzepithel* of Hürthle be seen and then it seemed obvious that it was the effect of mechanical dislodgement and disarrangement of the cells. Similarly the extensive desquamation of the epithelial cells which one so often sees in specimens removed at operation seems to be due to the considerable pinching and handling through which the specimen unavoidably passes during the operation. Nevertheless, we have met with one or two cases in which, in association with especially severe symptoms, there has been found widespread desquamation of the epithelium, probably not the result of pinching the gland, and this is regarded by some, especially by Dr. Bloodgood, as a feature associated particularly with very severe symptoms.

It is in these extreme cases that peculiar alterations of the epithelial cells are sometimes found. In several instances we have observed areas in which the epithelium was enormously swollen so as to practically obliterate the lumen of the alveolus. These large irregular cells no longer preserve the columnar form, but are shapeless masses of finely granular protoplasm which takes an intense pink stain with the eosin and in which the nuclei are also irregular in form and size and stain very deeply, almost black, with the hematoxylin. Usually one or two alveoli only show such a change in their epithelium, or there may be only a few cells of this form intercalated among others of the usual type in the alveolar wall, but sometimes over considerable areas all the alveoli are packed with such cells. Their significance is far from clear. Much more frequently there are found cells among the ordinary epithelial cells of the alveolar wall which are greatly enlarged but the protoplasm of which retains the characters seen in the rest of the cells and contains only a scant basophilic granulation. The nuclei of such cells are usually much enlarged and vesicular, with scattered chromatin granules.

The colloid varies greatly in different cases, but it seems that in most of the more severe cases it is markedly diminished in amount and altered in quality, the normal hyaline material being replaced by a very palely staining substance or by a ragged, shreddy, granular or vacuolated mass which has no longer the refractive qualities of the normal colloid. There are some cases, however, in which there is a great deal of fairly normal looking colloid, and this is especially true of those instances in which the hypertrophy of the epithelium is relatively slight: cases, that is, in which the process is apparently advanced, at least as far as the thyroid is concerned. On the other hand, when the colloid is greatly diminished one rarely fails to find severe symptoms, and when the symptoms are very indefinite or in part absent it is usual to find a good deal of colloid.

The most interesting cases in this connection, then, are those in which intense symptoms exist but in which at the same time the alveoli contain a large amount of colloid. There are at least twelve of these cases in our series, and although in some of them one may explain the existence of such large alveoli full of colloid, on the idea that the exophthalmic symptoms are associated with changes which have appeared in a gland already the seat of alterations such as are seen in a colloid goiter, still there remain many in which there is no evidence of such a previous goitrous change. From this it appears that the presence of quite abundant colloid is not inconsistent with the development of intense symptoms, although in most cases in which the symptoms are intense the colloid tends to disappear with the advance in the alterations in the gland. It is not improbable that the amount of colloid may bear a fairly constant relation to the stage of progress of the disease, and light may be thrown on this by the consideration of the tissues removed at successive operations. One can distinguish, however, different types of change in the thyroid in different cases, for while in one group the alveoli are not larger than normal, show elevation and folding of the epithelium and are full of colloid, another group with quite as intense symptoms will present thyroid tissue composed of very large alveoli full of colloid in which, nevertheless, the folding of the epithelial layer is most complicated. A third group comprises those cases usually milder in their course in which the alveoli are large and full of colloid but in which the alveolar epithelium is almost flat, except in certain foci or in portions of some of the alveolar walls where it becomes cylindrical and thrown up into folds. Several of the cases in which extirpation of the thyroid was carried out with good results for the relief of indefinite symptoms, such as the combination of goiter with tremor only or with moderate tachycardia only, showed in the thyroid abundant colloid in large alveoli which are hardly at all irregular,

but nevertheless in places show areas of epithelium which has become high and cylindrical and which is beginning to project prominently into the alveolar lumen.

Finally, in a few of the cases in which the symptoms were reduced to nervousness or slight tremor with goiter, the excised tissue shows the normal structure or that of a circumscribed adenoma. There were six of these cases which should be ruled out of the series.

The focal nature of the alterations in the thyroid is especially interesting and may be recognized in some cases in the fresh cut surface of the gland by the opacity and granular surface of the altered areas which contrast with the surrounding tissue. Apparently this, too, represents a stage in the development of the lesion, and in most of the six cases which show it the symptoms had existed only a short time before the operation. Microscopically the altered areas are quite sharply demarcated from the rest and may involve a great number of alveoli or be limited to very small foci, including only a few alveoli here and there. It is difficult to understand why the lesion should appear thus in certain areas only.

In sixteen of the cases there were found on cutting through the thyroid rounded circumscribed nodules which projected above the general level and differed in consistency and general appearance from the rest of the gland. These are the adenomatous nodules which constitute a considerable proportion of ordinary goiter, and hence they are by no means peculiar nor characteristic of the changes in exophthalmic goiter. They are most commonly finely granular and opaque, occasionally flecked with yellow patches of necrosis or with hemorrhages, and on section they are seen to be composed of small round alveoli lying quite separate from one another in an abundant loose stroma and lined with cubical epithelium. In only a few of our cases did the alveoli which make up such embedded nodules show the folding and other hypertrophic changes which characterize the tissue round about, but in one case in which ex-

ophthalmic symptoms were well marked these changes were limited to the tissue forming such a circumscribed nodule. In another case the hypertrophied tissue was found to form the thick lining of a cyst.

The second type of circumscribed nodule is that which is composed of a tissue very rich in colloid and correspondingly translucent. The central part is often occupied by a cyst-like cavity filled with a greenish glutinous fluid. Such nodules show microscopically very large alveoli more or less radially arranged and distended with colloid. The amount of fibrous tissue traversing the gland varies in different cases, sometimes occurring in coarse bands that separate the tissue into lobules, while in other cases there are, in addition, fibers which separate the individual alveoli.

In six of our cases it was possible to study the thyroid at different stages in the progress of the disease, either in tissue removed at two different operations or at autopsy in patients who died some time after the operation. No very constant results were obtained. In four of the cases, in which the intervals between the times of obtaining the two specimens were seven months, eighteen months, forty-five days and seventy-nine days, the tissues were practically identical in the two portions examined. In the fifth case, after a lapse of nine months, the tissue from the second operation showed that the epithelial cells had become greatly increased in height and the colloid rather more abundant. In the case in which the longest interval elapsed between the operations, two years and six months, the alveoli had changed from small compact almost solid masses of epithelium with inconspicuous lumen and no colloid to large ramifying spaces full of ragged colloid and lined with very high cylindrical epithelium.

Thus in these cases there is no tendency in the thyroid toward a return to the normal, nor should we expect it, since the second portion of tissue was obtained either after death in cases in which the symptoms had per-

sisted or at an operation undertaken because of the persistent symptoms. It will be extremely interesting to investigate the thyroid in one of the cases in which amelioration or cure of the disease has followed partial excision, if opportunity ever presents itself.

In this connection, too, those cases seem important in which the symptoms of exophthalmic goiter have gradually given place to those of myxedema with atrophy of the thyroid.

In nearly all the typical cases there are scattered about, usually in connection with the fibrous strands, masses of lymphoid tissue which are sometimes large enough to be conspicuous, opaque white dots visible in the fresh specimen. In one instance in which there was a cyst the numerous lymphoid nodules shone through the wall of the cyst very distinctly. In some cases they are small and indefinite in outline and are composed of an irregular accumulation of lymphoid cells. Generally, however, they are well-formed lymphoid nodules with very distinct germinal centers, composed of concentrically-arranged cells with abundant protoplasm. It seems probable that this increase in the bulk of the lymphoid tissue, which is practically invisible in the normal gland, is part of the general increase in size of the lymphoid structures of the neck which occurs so often.

This could be studied in a few of the cases at autopsy in which it was found that the lymph glands and hemolymph glands were enlarged, especially in the neck, but also in the thorax, abdomen and retroperitoneal region. The superficial glands are usually not so much enlarged, but the lymphoid tissue in the pharynx, the tonsils and the nodules in the tongue become very conspicuous. Microscopically it is found in all these places, as in the lymphoid nodules of the thyroid itself, that there is a great increase in the lymphoid cells, but also that the germinal centers become very large and sharply outlined and contain many actively phagocytic cells. The sin-

uses are usually filled with wandering cells. This change in the lymphoid tissue has the appearance of being a reaction to the absorption of some poisonous or injurious material, but whether this material stirs up the thyroid also to proliferation or is itself the product of the overactive thyroid is difficult to say.

The thymus, too, has been found by nearly all investigators to be enlarged. There are not only the usual scanty remains, but the mass of tissue is frequently seen to be as large or larger than that seen in a child before retrogression has taken place. Histologically it has the same appearance as in those earlier years, and the same processes of phagocytosis are seen to be going on. The recent statements as to its epithelial nature make this change in the thymus especially interesting and deserving of more attention than has been accorded it, particularly since there have been some favorable results from the administration of thymus extract in this disease.

The parathyroid glands are sometimes to be found attached to the portion of the thyroid extirpated at operation, even when the greatest care is exercised to preserve them. In other instances they were found at autopsy, and altogether we have had the opportunity of studying them in sixteen cases. They were practically normal in all the cases. The cells of all varieties found in the normal gland were seen in these, too, in the usual proportions. In six of the cases the notes state that there was an increase in the fibrous stroma, and renewed examination of these glands shows that there is in some cases a network of scar tissue running through the tissue, just as has been seen in the thyroid in so many of these cases. Otherwise, however, the tissue in these glands seems abundant and normal. On the whole it seems improbable that the parathyroids have anything to do with the production of the symptom-complex of exophthalmic goiter when we compare these very slight

anatomic lesions with the advanced changes in the thyroid.

Much attention has been devoted to the study of the cervical sympathetic ganglia and nerves, since the idea is held by many that changes in those structures are really at the bottom of the whole disease, but the results of these studies have been very unsatisfactory; some authors have described atrophy of the cells, increase in the pigment or overgrowth of connective tissue, but quite as many or more have found the ganglia perfectly normal. We have studied them carefully in two cases and have found no pathologic alterations, unless the presence of a number of shrunken deeply-stained ganglion cells in one section can be regarded as pathologic. This ganglion was fixed in formalin and the one from the other side in alcohol. In that one no such changes were found, so that I am not disposed to attach much importance to them.

Similar results have come from the anatomic studies of the central nervous system, for while in some cases atrophy or destructive lesions have been found in the corpora restiformia, and in others hemorrhages in the medulla, the majority have shown no abnormality, and at best the lesions must be regarded as extremely inconstant.

As to the hypophysis cerebri, there seems to be few recorded observations. Hämig studied it in nine cases and found it quite normal, although in several of the cases the number of chromophile cells were striking. In the one case in which we have secured the hypophysis its tissue was normal.

Of pathologic alterations in other tissues and organs so little is known and the findings are so inconstant that they may well be passed over.

On the whole, therefore, the only lesions in this disease which are palpable and constant are those of the thyroid and of the lymphoid apparatus and thymus. All of the others are so indefinite and so often completely

missed that it is difficult to convince oneself that they play a primary rôle in the disease.

From what has been said it is seen that with the appearance of definite symptoms of exophthalmic goiter there is always the same change in the thyroid. In very mild and indefinite cases it may be possible to find only the beginning of this change in some part of the walls of some of the alveoli. In more severe cases in the early stages the change in the thyroid may be in foci only, while the rest remains normal, but in the more advanced cases the typical change with proliferation of the epithelium and folding of the walls of the alveoli is invariably found. None of our cases came from goiter regions, although one or two had goiters before the exophthalmic symptoms developed. Even in these it is only necessary to look far enough to find the changes described above superimposed on those of the old goiter. Sometimes in nodular goiters only the intervening tissue shows the hypertrophy well, but in other cases that of the adenomatous nodules will also show it. From this series of cases we are quite convinced that this change in the thyroid in a more or less complete development is quite constantly associated with the symptoms of exophthalmic goiter.

Now this is anatomically the change produced in compensatory hypertrophy when we excise part of the normal gland, but that compensatory hypertrophy never produces a mass of tissue in excess of the normal and no symptoms result. It is the same change, too, that we find in sheep and dogs, sometimes with very marked enlargement of the thyroid, but these animals show no definite symptoms, or if they do they are rather the symptoms of myxedema (Marine). There can not be a complete analogy, then, between these lesions. In exophthalmic goiter there must be something more than the mere hypertrophy of the thyroid, either in the nature of its secretion or in some other factor quite aside from the thyroid. Nevertheless it is certain enough that the

thyroid is hypertrophied and the current opinion is that it is functionally overactive and producing an excess of secretion. This, however, remains to be directly proven, and Oswald, in opposition to the general view, believes that we really have there a condition of thyroid insufficiency, since the gland is often nearly empty of colloid and contains relatively little iodin-holding secretion. But the removal of part of the thyroid improves the symptoms of the disease, and the administration of thyroid extract makes them worse, so that we are almost forced to the belief that the excessive activity of the thyroid is at fault.

The great question seems to remain: if the gland is hypertrophied and overactive, what has caused this hypertrophy? The symptoms of exophthalmic goiter are so like those of artificial thyroidism that it is fairly easy to believe that there is this exeessive activity and that the other symptoms depend on the outpouring from the thyroid. But we have no examples elsewhere of the spontaneous hypertrophy and overactivity of an organ to the detriment of the rest of the body. Always it is a work hypertrophy or compensatory hypertrophy, but here the inconsistency appears that when you excise part of this hypertrophied gland the symptoms often disappear.

Is it possible that the fundamental underlying cause is some infection, such as influenza, which, reaching the thyroid through the pharynx, sets up such a non-suppurative thyroiditis as has been described by de Quervain, destroying many of the cells and leaving scars through the gland, after which the remainder becomes hypertrophied and its activities perverted? Gilbert and Castaigne, Reinhold, Breuer and others describe such a course of events, and, indeed, a history of pharyngitis or grip is very common as a forerunner of this disease. It is still rather hard to comprehend the overstepping of the normal to such an extent in the process of compensatory regeneration, and the production of a harmful

organ by a mechanism which usually restores to normal with such precision.

The relation of iodin to this disease is interesting, for while in a normal person the symptoms of iodism do not very closely resemble those of exophthalmic goiter, it is claimed by Breuer that in cases of exophthalmic goiter the symptoms may be made much worse or latent symptoms called out by administration of iodids.

Further, the suggestion may be offered that it is possible, since some of the symptoms are generally referred to disturbances of function of the cervical sympathetic system, that the vasoconstrictor influence of those ganglia over the thyroid may be diminished and that a consequent hyperemia of the gland may finally bring about an overactivity. Attempts to study this experimentally by the isolation of the thyroid from all nervous connections, even those which are closely bound up with the vessels, have so far led to no result.

Since the most palpable and constant change in this disease is after all in the thyroid, it seems that our efforts to explain the disease must start with the explanation of the disturbances in structure and function of the thyroid. We must know definitely whether it is pouring out an excessive secretion into the circulation; we must be able to recognize that secretion and estimate its amount and its toxic character. Then we must learn surely whether the thyroid is doing this independently or whether it is in response to some disturbance in metabolism elsewhere. It seems possible even that it might be in response to a demand only for some other associated substance which brings with it the toxic substance, so that while the thyroid hypertrophies to meet a justifiable demand it incidentally produces a noxious substance in excess.

At all events, we must learn the underlying cause of these changes and not be content with discovering which organ is most disturbed, for only in that way can a perfectly rational therapy be devised.

THE DIAGNOSIS OF EXOPHTHALMIC GOITER.

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The part assigned to me in this symposium is the diagnosis of this remarkable disease. What I shall have to say is based (1) on an analysis of the cases which have occurred in my wards at the Johns Hopkins Hospital during the past two years,[1] and (2) on a study of the bibliography of the subject.[2]

It will be convenient to discuss (I) the character and significance of the individual signs and symptoms; (II) the diagnosis of the clinical syndrome, especially in its less obvious forms; (III) certain points in differential diagnosis, and (IV) the diagnosis of the indications and contraindications for surgical interference.

On account of the necessity of brevity I am forced to limit the discussion to the features which I regard as most essential.

I. THE CHARACTER AND SIGNIFICANCE OF THE INDIVIDUAL SIGNS AND SYMPTOMS.

Besides the three cardinal symptoms—struma, tachycardia and exophthalmus—there are a very large number of other symptoms and signs to be considered, some of

1. I have to thank Drs. Roger Morris and Benson A. Cohoe for help in the analysis of the material.

2. Especially helpful articles are: Moebius (P. J.): Die Basedow'sche Krankheit., Wien, 1896; a new edition has recently appeared with a very full bibliography. Buschan (G.): Die Basedow'sche Krankheit., Eine Monographie, 8°, Leipsig u. Wien, 1894. Kocher (A.): Ueber Morbus Basedowi, Mitt. a. d. Grenzgeb. d. Med. u. Chir., Jena, 1902; ix, 1-304. Dock (G.): Clinical observations in exophthalmic goiter, Am. Med., Phila., 1906, xi, 271-281. Kocher (T.): A contribution to the pathology of the thyroid gland, Brit. Med. Jour., Lond., 1906, i, 1261-1266.

them more important than the exophthalmus as diagnostic aids because more frequent and characteristic.

A. THE STRUMA OR GOITER.

The thyreoid gland is enlarged in the majority of cases of the disease. Since we have been taught how to recognize slight enlargements, the reports of exophthalmic goiter without goiter have grown fewer, and some go so far as to deny the existence of an exophthalmic goiter without struma. It does exist, however. In twenty-one of my cases a struma was recorded in the notes dictated at the ward rounds in eighteen. The whole gland is, as a rule, uniformly involved, giving rise to the well-known horseshoe-shaped projection, but one lobe may be larger than the other. The struma is not large as a rule; the patient may even not have noticed the thickening of the neck. The isthmus of the gland is usually broadened and thickened and the pyramidal lobe is enlarged. The consistence varies according to the stage of the disease and according to the acuteness or chronicity of its course. At the beginning and in cases running an acute course it is often softer than normal; later on, and in chronic cases, the consistence is firmer and more elastic. A characteristic feature is the granulation of the surface, usually easily recognizable on palpation and due to the lobular hyperplasia. Most important, from the diagnostic standpoint, are the vascular peculiarities of the goiter. The typical struma in exophthalmic goiter is always a struma vasculosa. The telangiectasis is recognizable (1) by the visible pulsation of the goiter, (2) in many instances by the palpable systolic expansion, (3) by the palpable thrill, and (4) by bruits audible at the point of entrance of the thyreoid arteries (especially the superior) into the gland. The struma, though usually recognizable by the educated touch of the physician's finger early in the disease, is mentioned by only about one-fifth of the patients as preceding the other symptoms.

B. THE TACHYCARDIA OR (BETTER) PYCNOCARDIA.

In the semiotic trinity the increased frequency of the heart beat is the most constant and most important sign. The pulse rate is practically always over 90 and may exceed 200 beats to the minute. A rate between 110 and 150 is very common, and the patients usually notice subjective palpitation; sometimes they complain of it bitterly. In my experience this exquisite thyreotoxic phenomenon is usually continuous and persistent. In a few cases, however, I have seen it irregularly or intermittently present. In one it was always precipitable in the early part of the disease by psychic influences and became continuous later. Very rarely pycnocardia is absent when other signs of the disease are present, and then, as Dr. Emerson has shown, the sign may sometimes be brought out by the administration of a few doses of thyroid tablets.

C. THE EXOPHTHALMUS.

This sign is the most striking of all to the casual observer when it is present. It is entirely absent in about one-third of the cases, and even in many of the other two-thirds it may be so slight as not to attract attention. It is necessary to distinguish between apparent exophthalmus due merely to widening of the palpebral fissure and true protrusion objectively demonstrable as a shortening of the distance between the supraorbital margin of the frontal bone and the anterior pole of the eyeball (measurement with exophthalmometer). The former is, as a rule, a more important factor in the changed facial appearance than the latter. The prominence is usually bilateral and continuous; it may be unilateral and the intensity may vary from time to time.

D. PHENOMENA PERTAINING TO THE MUSCULAR SYSTEM.

The tremor noted by Trousseau and Charcot really ranks in diagnostic importance along with the pycnocardia and the struma; it is so frequently present that one inclines with Marie to designate it as a fourth

cardinal sign. The tremor is rapid and vibratory, there being as many as eight to ten oscillations per second, in marked contrast with the slow tremor of paralysis agitans. It is best seen by asking the patient to hold his hand with widespread fingers between the observer and the light. The tremor may be limited to the extremities, but frequently involves also the muscles of the neck and trunk. It is not exaggerated by voluntary movement, but is increased by psychic excitation. Paresis, paralysis or atrophy are occasionally seen. In how far they are related to the fatty change in the muscles described by Askanazy is not known. Sudden "giving way of the legs" may be an early symptom.

E. PHENOMENA PERTAINING TO THE DIGESTIVE APPARATUS.

Diarrhea and vomiting, both without apparent cause, are not infrequently troublesome symptoms in advanced stages of the disease. They are rare, however, at the beginning and are, therefore, of little help for diagnosis. Other abnormal phenomena, noticeable in the digestive apparatus, are too rare and inconstant to be of much diagnostic value.

F. PHENOMENA PERTAINING TO THE RESPIRATORY APPARATUS.

Here dyspnea is the most important phenomenon. It is usually a late symptom, present in relatively few cases, and generally cardiac in origin.

The respiratory curve as recorded by graphic methods is flattened (Hofbauer). The lessened expansion of the thorax (Bryson's sign) is probably due to weakened muscles and is of no special diagnostic importance.

I would call attention to air-hunger and the peculiar fruity odor of the breath occasionally present in advanced cases; these are important, not for the diagnosis of the disease itself but as indicating the existence of acidosis which may call for an immediate therapeutic effort.

G. PHENOMENA PERTAINING TO THE UROGENITAL APPARATUS.

Here there are no constant findings. Polyuria, glycosuria, transient albuminuria are only occasionally met with. The urea-nitrogen, the total nitrogen, the uric acid and the phosphates of the urine are increased corresponding to the accelerated metabolism in this disease. A diminution of the menstrual flow is a very common accompaniment of exophthalmic goiter in women. The breasts occasionally show changes, usually of rejuvenation.

H. PHENOMENA PERTAINING TO THE CIRCULATORY APPARATUS.

The pycnocardia, the most helpful of the signs for diagnosis, has already been mentioned. But the heart shows other changes also. The heart sounds are strongly accentuated, and accidental systolic murmurs, due to the excited and accelerated action of the heart, are frequently audible both at apex and base. The right ventricle appears to be especially affected, and its excited action can be recognized by palpation to the left of the sternum. In advanced cases the heart is not infrequently dilated. The cardiac condition varies with the intensity of the thyreointoxication, and is a valuable criterion for judging of the latter.

The radial pulse is usually small and quick. Arrhythmia is rare except in advanced cases or where the heart is otherwise diseased. The maximal arterial pressure varies. It is sometimes low, but more often higher than normal, and occasionally very high. The pulse pressure (difference between maximal and minimal pressure) may be large, indicating a large systolic output from the left ventricle. When this is borne in mind along with the great increase in the heart rate one begins to realize the amount of work done by the heart in this disease.

Throbbing of the carotids and of the abdominal aorta

is a sign frequently present, and one of considerable diagnostic import.

Slight edema of the legs, hands or eyelids is common.

The blood shows no constant alterations, though a relative increase in the mononuclear white elements has been noted by some in the differential count.

The slight enlargement of the lymph glands of the neck so constantly seen at operations is only rarely demonstrable clinically by palpation.

I. PHENOMENA PERTAINING TO THE NERVOUS SYSTEM, SENSE ORGANS AND SKIN.

Both the cerebrospinal and sympathetic nervous systems are profoundly affected in the disease, the involvement of the autonomic systems, especially the bulbar, being perhaps most marked. It is surprising how many of the phenomena pertaining to the other parts of the body may conceivably be brought into relation with disturbances of the autonomic neurone-systems.

The psychic manifestations are often pronounced and may be the first to excite suspicion as to the diagnosis. Feelings of restlessness and discomfort, an indefinable anxiety or apprehension without cause and rapidly alternating moods are very characteristic. One of my patients gradually became so irritable and violent that his wife, not knowing the cause, had him before a magistrate and bound over to keep the peace. Another became so anxious and disturbed that she lost confidence in herself and had to be sent temporarily to a closed institution pending the passing of the psychosis. Even hallucinations or persecutory ideas may develop. Insomnia is frequent and headache also. Vertigo is less common, delirium rare. Pains in the neck or jaws, and shooting pains in various parts of the body are occasionally complained of. A subjective sensation of heat in the body, independent of fever or of the external temperature, is a common symptom. At the beginning of the disease a feeling of weakness, so strong as to inter-

fere with work, is present in many cases; easy fatigability, in young people especially, should excite suspicion.

The eye signs are among the most interesting. The pupils are usually equal and react to light, though with unilateral exophthalmus one pupil may be larger than the other. Aside from the exophthalmus and widening of the palpebral fissure, the most important signs here are (1) the failure of the upper eyelid to follow the eyeball normally in looking downward (v. Graefe); (2) the retraction of the upper lid on straight-forward vision, revealing some sclera above cornea (v. Stellwag; Dalrymple); (3) the infrequent and incomplete involuntary winking (v. Stellwag); and (4) the inability to hold the eyes in the position of convergence (Moebius). Other signs such as (5) the difficulty of everting the upper lids (Gifford); (6) the pigmentation of the upper lids (Jellinek and Rosin); (7) the failure of the forehead to wrinkle on looking up (Joffroy); (8) epiphora or overflow of tears; (9) the tremor of the eyeballs; (10) the subjective feeling of pressure behind the eyes (A. Kocher); and (11) abnormal dryness of the eyes, are occasionally met with. These signs, dubbed "fancy signs" by my colleague, Dr. Thomas, who fears a neglect of the cardinal tetrad through a search for the novel, are not without their diagnostic value; the presence or absence of all eleven may be determined in a few moments and a clue quickly gained to the unraveling of a condition which might, otherwise, easily escape detection.

The organs of hearing, smell and taste rarely present abnormal symptoms or signs. In the integumentum commune, however, important phenomena are observable. The skin is nearly always smooth, delicate, thin and moist. Sweating is constant and troublesome in a majority of the cases and accounts for the well-known increased electric conductivity of the skin (Vigouroux's sign). Vasomotor instability in the skin is a prominent feature, and the physician when making his first phys-

ical examination of the patient is often struck by the blotchy erythema of the neck and upper chest. Pigmentation is the other most important cutaneous sign; the color of the skin may resemble that seen in pernicious anemia, or it may approach that of Addison's disease. The nature of this pigmentation may perhaps not be understood until we are better informed regarding the chromaffine systems of the body. Falling of the hair is more common than prematurely gray hair (canities præmatura), though both are met with.

K. PHENOMENA PERTAINING TO THE GENERAL METABOLISM.

Clinicians have long since noticed the marked tendency to emaciation despite liberal feeding in exophthalmic goiter. A loss of from 20 to 50 pounds in weight during a short period is not uncommon. The body-weight curve is important as a clue to the speed of the metabolic reactions, and thus for judging of the intensity of the disease. The metabolic disturbance consists of an acceleration of the oxidative processes (Fr. Müller; Magnus-Levy); in doubtful cases in hospitals a determination of the oxygen intake and of the CO_2 output by the Zuntz-Geppert method is a diagnostic aid, though it is too inconvenient for use in private practice.

The occurrence of mellituria in the disease has already been referred to. Slight fever was noticed in several of my cases. Whether or not such fever is due to a disturbance of heat-regulation, which is a part of the disease proper, is not known. It may depend on complications.

II. THE DIAGNOSIS OF THE CLINICAL SYNDROME, ESPECIALLY IN ITS LESS OBVIOUS FORMS.

The diagnosis in typical cases of the well-developed disease could scarcely be overlooked except by an untrained or superficial observer. The coexistence of pycnocardia, struma and tremor, with or without exophthalmus, are decisive. It is in the beginning of the dis-

ease and in the atypical cases, including the so-called *formes frustes,* that some difficulty may be encountered. Once the clinician, however, has learned to recognize a beginning struma vasculosa, and to realize the significance of the so-called hyperthyreotic equivalents, especially the thyreotoxic form of the goiter-heart, the thyreotoxic neuropathic and psychopathic states, and the thyreotoxic acceleration of oxidative metabolism, he will rarely be left in doubt. It may in some instances be possible to unmask a latent hyperthyreodism by the administration of a few doses of iodothyrin or by a Zuntz-Geppert estimation. It should be borne in mind that nearly all the phenomena of hyperthyreoidism are accentuated somewhat by the recumbent position; this may explain why the patients so often feel worse in the morning than after they have been up and about during the day. It is unusual, even in the mildest forms, not to get at least some hint from the eyes, if the various tests be run through.

III. CERTAIN POINTS IN DIFFERENTIAL DIAGNOSIS.

A few words must be said concerning the differential diagnosis as regards (a) strumata, (b) goiter-hearts, (c) exophthalmus, (d) thyreotoxic pseudochlorosis, and (e) the conditions underlying hyperthyreosis and accounting for it.

(*a*) *Strumata.*—(1) Not every acutely developing pulsating struma is an exophthalmic struma; (2) the symptoms of exophthalmic goiter may become superimposed on an ordinary colloid struma, in which event the thyreotoxic symptoms appear to be mitigated (*goitre Basedowifié* of Marie, *struma Gravesiana colloides* or *struma Basedowificata* of Kocher).

(*b*) *Goiter-hearts.*—It seems tolerably clear that the goiter-heart of exophthalmic goiter is a thyreotoxic phenomenon. With Friedrich Müller, I can see no reason for separating from it the milder forms of the thyreotoxic heart (*Kropfherz* of Kraus; *Kardiopathia thyreogenes levis* of His). There is every transition from the

conditions in which they occur to the outspoken state. There is force, however, in the argument that the cardiopathies due to the mechanical effect of a goiter (Minnich) be separated from the thyreotoxic goiter-heart. Thus (1) disturbances of the heart due to strumata extending through the superior aperture of the thorax (Kocher), (2) the goiter-heart due to mechanical injury of the venous circulation (Rose's goiter-heart), and (3) that due to interference with respiration (dyspneic goiter-heart of Kocher), would come in this class. Though thyreointoxication may play a secondary part in such cases, it is the diagnosis of the mechanical injury that is all important and should guide the therapy.

(*c*) *Exophthalmus.*—It is usually easy to distinguish the exophthalmus of this disease from other forms of exophthalmus, but mistakes are sometimes made. Protrusion of the eyeballs due to the increase of intracranial pressure (especially in hydrocephalus), to aneurism, sinus thrombosis or abscess (unilateral exophthalmus), or to retrobulbar growths, especially chloromatous masses (Dock) should be remembered. An acute recurrent exophahtlmus due to angioneurotic edema has also been described (Gruss).

(*d*) *Thyreotoxic Pesudochlorosis.* — Wunderlich observed protrusion of the eyeballs in anemic-looking girls. This is often associated with pallor, fatigability, emaciation and accelerated heart action. It was supposed to be due to chlorosis, and the goiter is mentioned in medical writings as a struma chloroticum. Blood examination shows, however, the presence of a normal or excessive amount of hemoglobin, and such patients are doubtless affected with true exophthalmic goiter (Fr. Müller). When they begin to lose weight, to have slight fever and to sweat freely the suspicion of pulmonary tuberculosis may be aroused. Dr. A. D. Atkinson, of Baltimore, recently showed me such a patient; a rapid tremor, a pycnocardia, a suggestive v. Graefe's sign, a normal blood-count and slight enlargement of the thy-

reoid gland helped to make a diagnosis of hyperthyreoidism certain.

(*e*) *Conditions Underlying Hyperthyreosis.*—Though it is now possible for us as internists to recognize hyperthyreoidism in its very early stages, we realize fully that we are far from understanding the causes of the hyperthyreosis. Hyperthyreosis, like jaundice or fever, may be excited by different causes, and we must from now on try to make out the varying etiology, be it toxic, infectious, reflex, obscure metabolic or still other in nature. In one case recently reported a hyperthyreoidism developed as a result of a metastatic endothelioma in the gland. This raises the questions concerning the justification of the terms "Basedow" and "Pseudobasedow" (Buschan) and of "essential" and "symptomatic" exophthalmic goiter (Moebius), questions which can not well be answered until we have further knowledge.

IV. THE DIAGNOSIS OF THE INDICATIONS AND CONTRAINDICATIONS FOR SURGICAL INTERFERENCE.

An important part of the physician's function lies in the diagnosis of the indications and contraindications for surgical interference. Formerly surgery was resorted to only after non-surgical treatment had been given a prolonged trial without success. The brilliant results of surgical treatment in the earlier and milder forms of the disease (Halsted, Horsley, Kocher, v. Eiselsberg), make it incumbent on medical men to consider operation early and seriously. Though nearly all patients improve on rest, a diet which does not stimulate the thyreoid (milk), sodium phosphate and fortnightly *x*-ray exposures, and although occasionally a patient will get well, very many go backward again as soon as treatment is discontinued. In the very early cases surgery is capable of curing nearly 100 per cent.; even in the outspoken cases almost 75 per cent. can be cured by operations judiciously planned and skilfully performed, and the mortality, now about 5 per cent., can be further reduced Internal medicine up to this time

has been utterly unable to obtain results comparable with these. In the present state of knowledge and practice, therefore, once a positive diagnosis of exophthalmic goiter has been made, it is, in my opinion, the physician's duty and privilege to recommend operation early. I do not say that every patient presenting the v. Graefe phenomenon or an irritable heart should be operated on, but when a persistent pycnocardia associated with a vascular struma has been discovered, or whenever the grouping of symptoms is such as to leave no doubt of the existence of a persisting thyreointoxication, medical treatment, unless markedly beneficial, should not be continued long before operation is advised. The only contraindications in uncomplicated cases are a feeble heart with very high pulse frequency or pronounced psychic excitation; when these are present a brief preliminary medical treatment may be necessary; if the serious symptoms persist in spite of it and indicatio vitalis exist, the dangers should be pointed out and operation resorted to.

And just here a heavy responsibility rests on the physician. Fully as important as the diagnosis of the indication for operation is the choice of the surgeon. The physician should select an operator thoroughly familiar with the anatomy and pathology of the thyreoid and para-thyreoid glands and skilled in the special technic required. Success depends so largely on the formation of a correct judgment as to the amount of the gland to be removed and as to its removal in one or several operations, that the physician must be sure of his surgeon. Aside from the dangers of tetany, if too much gland is removed, hypothyreoidism will result and the patient be doomed to thyreoid-eating or an implantation; if too little (a less serious matter) more of the gland can be taken out later. One thing seems established, that in exophthalmic goiter the symptoms retrogress in exact conformity with the amount of thyreoid extirpated.

At present there is a fair prospect that the treatment

of the disease may again be transferred from the surgeons to the physicians. The remarkable results already obtained in a number of cases by Rogers and Beebe through the use of their curative serum give us good reason to hope that a method will ultimately be perfected which will permit the internist to accomplish with his needle what he now asks the surgeon to do with the knife.

MEDICAL TREATMENT OF EXOPHTHALMIC GOITER.

ROBERT B. PREBLE, M.D.
CHICAGO.

A correct estimation of the value of any plan of treatment of a given disease is easy or difficult, possible or impossible, in direct proportion to the closeness with which the disease follows a type. If the disease is acute and typical, the therapeutic value of any measure is readily determined; but if, on the contrary, the course of the disease is chronic and subject to the many spontaneous remissions and exacerbations, it is nearly impossible to reach a just estimate of the value of any plan of treatment. When, in addition to these characteristics, the pathologic phenomena are not sharply separated from physiologic processes, the difficulties opposed to correct judgment are further increased. There is perhaps no disease, the history of which better demonstrates the truth of these principles, than does exophthalmic goiter. An almost unending list of plans of treatment might be prepared and in regard to each the opinions of their value have varied from useful, through useless, to harmful. And to-day, although there are many reasons for the belief that we are at last approaching an adequate conception of this disease, there still reigns the greatest chaos in its treatment, and so far as I can see there will continue to be great diversity of opinion on the subject until our knowledge of its pathology, and particularly of its etiology, becomes more complete than it is at present.

It is difficult, indeed impossible, to even sketch the various things which may be done for the patient in the time allotted, and it is not likely that it would prove to be profitable. It, therefore, has seemed best to make an effort to group the various plans as follows:

1. Those directed toward the correction of the neurosis, which is believed by many to lie back of and to cause the alteration in the functions of the thyroid gland.

2. Those which are directed toward counteracting the perversion of the thyroid secretion.

There is much collateral evidence in support of the idea that fundamentally this disease is a neurosis, and independently of whether this is true or not a very considerable proportion of the patients must be or are, at least for a time, best treated along these lines.

One of the most important and constant of the symptoms is the increase in tissue waste, a fact which immediately suggests the advisability of rest and of abundant proper nutrition. The degree of rest required varies in different patients and in the same patient from time to time, and ranges from absolute and prolonged rest in bed to a mere restriction of activities. The rest should be both physical and mental. In many instances this rest, particularly the mental rest, can be best obtained if the patient is in hospital or sanitarium. In other instances, however, the opposite is true, just as in some cases a certain amount of work may be permitted. It is not possible to give more than the most general suggestions on these points, and much must be left to the judgment and good sense of the physician in charge. The better his suggestions are adapted to the individual case and her surroundings, the more satisfactory the results will be.

So, too, in regard to the diet, thought and care are necessary. The circumstances, tastes and digestive powers of each case must be consulted. In some cases forced feeding is required, while in others the usual amounts of food are sufficient.

The influence of climate is often important and many cases are greatly benefited by a change. Just what change should be advised can not be stated, for, while some cases are improved by a trip to the mountains, others receive greater benefit from a trip to seacoast or an ocean voyage. If the cardiac symptoms are marked, high elevations should be avoided; and, if the patient goes to the seashore, surf bathing should be forbidden. And, wherever the patient goes, quiet, rest and good food are absolutely essential.

These general hygienic and dietetic suggestions, suitable under all circumstances and to all cases, may be combined with various other measures, such as baths, massage and electricity.

Baths of various sorts and kinds have been very enthusiastically advocated by those whose interests are centered in hydrotherapeutic methods and institutions, but, when sufficient allowance is made for this enthusiasm, there is not much left to say in their favor.

Various forms of the electric current have been extensively employed; some advocate galvanism, some faradism, some the static current. There is much diversity of opinion as to their value. But it is probable that no one of them has other than a suggestive influence, and it should always be kept in mind that the exophthalmic patients are extremely susceptible to suggestion. This is well illustrated by the statement of Moebius to the effect that anything is of value, providing only that the patient is led to think that it is.

More recently some use has been made of the *x*-ray. Some have reported most favorable results from this method, while others have seen no other effects than a lessening of the activity of the metabolic processes.

Turning now to the question of drugs, one finds an almost unending list which have been employed, and in regard to the value of each one finds wide diversity of opinion. The use of various iron preparations has been advocated and condemned, but the summation of ex-

perience is that if there is an anemia, particularly one of the chlorotic type, as there often is, iron is useful, but that it has no direct effect on the fundamental process.

Arsenic is another drug about which much the same may be said as has just been said in regard to iron.

Iodids, the use of which is suggested by the presence of the goiter, have been used by many, and, while their use may be accompanied by a reduction in the size of the goiter, the other and more important symptoms are intensified. This is particularly true in the cases of primary exophthalmic goiter. There are some who have seen patients improve under their use, but in general it may be said that the improvement is in spite of rather than because of. For some reason yet unknown the iodid of potassium has proved to be more harmful than iodin itself. The use of iodothyrin is to be unreservedly condemned.

Because of the prominence of the cardiovascular symptoms, drugs which influence these have been extensively employed, in particular the digitalis. In regard to the value of this, as of its substitutes, strophanthus and convallaria, there is the same diversity of opinion noted in regard to all the agents so far mentioned. Small doses accomplish nothing, while larger doses are prone to excite the signs of digitalis poisoning. Many experiences and careful clinicians, however, employ these drugs in cases where there is extreme tachycardia or any of the usual evidences of cardiac insufficiency, such as cardiac dilatation, passive congestion of the liver or edema of the feet.

It has also been natural to endeavor to lessen the extreme nervous irritability of these patients by the use of various sedatives, the bromids in particular having been extensively employed. The bromids of sodium and potassium are the ones usually given, but the hydrobromate of quinin has also been advocated, even with enthusiasm, by some. Opium or its derivatives has been

used for years and, except for the dangerous possibility of establishing a drug habit, seems to me personally to be more valuable than other sedatives.

To these, the drugs most often employed, may be added others, such as quinin, antipyrin, phenacetin, salicylates, veratrum viride, aconite, cannabis indica, strychnia, nitrites, sodium phosphate.

One is forced by such a review as this, and by the diametrically opposed opinions which have been expressed by equally careful observers as to the value of each of the drugs or methods mentioned, that no one of them has any direct effect on the process and that their beneficial influence is determined solely by the skill and intelligence with which their use is adapted to each particular case.

Another group of preparations which have been used and still are to a limited extent, deserve mention more because it shows the evolution of our ideas as to the essential nature of the diseases. This group contains the bodies prepared from various glands having an internal secretion and includes the thyroid, thymus, suprarenals, ovaries and testicles. In regard to all of them one finds favorable reports, but, after reviewing the entire experience, one must conclude that they are all useless, with the exception of the thyroid preparations, which are positively harmful.

Lastly come the preparations which appear to best fit with the current idea that an excessive or perverted activity on the part of the thyroid gland is the essential factor of this disease. This belief, one which I personally share, has led to the manufacture of a number of antitoxic or cytotoxic preparations. While the fundamental idea underlying these is the same, the preparations are of two different sorts: first, those derived from animals which have suffered thyroidectomy, and, second, those derived from animals to which normal or pathologic glands have been administered. In a few instances the serum of patients with myxedema has

been employed, but it is obvious that no extensive use of this is possible. The preparations which have been most extensively used are the milk, either natural or desiccated, from thyroidectomized animals, the antithyroidin of Moebius, the thyroidectin, i. e., the desiccated blood of thyroidectomized sheep, and very recently a serum prepared by Rogers and Beebe by the use of the nucleoproteid and thyroglobulin from normal and pathologic glands.

It is yet too soon to express a definite and final opinion as to the value of these various so-called specific preparations. The reports so far published are to the effect that most of the cases are improved, a small number are cured and an equally small number are unaffected. Were it not for the apparently well-grounded theories which underlie this work, we would, I believe, be justified in saying that these preparations are as futile as the other methods of treatment which have been outlined, and that the cures and improvements are to be referred to the rest, hygiene and passage of time rather than to the material administered. However, no definite judgment on the question can be reached until more cases have been observed, more time has elapsed, and probably until more perfect sera are prepared.

After this discouraging review of the methods of medical treatment, it would seem as if all cases should be treated surgically, and yet I think that many, possibly a majority of the cases, should continue to be handled by medical methods, for one must always remember that the natural evolution of the disease is toward recovery. I have endeavored to formulate some rules which might serve as a guide to the selection of the cases for surgical treatment, but can not, even to my own satisfaction, go further than to say that medical treatment should be employed in every case until it is seen that, in spite of rest, proper nourishment and hygiene and intelligent effort at the correction of individual symptoms, the patient is steadily getting worse.

How long the employment of surgical measures should be delayed must be determined in each individual case, but it is far better to operate earlier than is necessary than to delay too long.

If in a given case the condition is not serious, but in spite of the best of help still remains bad enough to interfere with the usefulness of the individual, partial thyroidectomy should be employed.

The same thing must be said of the resection of the thyroid as has been said of the other methods of treatment—that the results are good or bad in direct proportion to the skill and intelligence with which it is advised and carried out.

THE SURGICAL TREATMENT OF EXOPHTHALMIC GOITER.

ALBERT KOCHER, M.D.
BERNE, SWITZERLAND.

Out of 3,460 operations for goiter performed in Professor Kocher's clinics in Berne up to date, 315 have been done on 254 patients afflicted with exophthalmic goiter, of which I will speak here.

My father, Theodor Kocher, was one of the first to operate on the thyroid gland in this disease, which he always claimed to be caused by hyperactivity of the thyroid. The results of his operations on the gland have been up to date so satisfactory that he has proceeded in very much the same way for the past twenty-five years.

I will say only a few words of other operations. In three excisions of the sympathetic nerve, to which I referred in my paper in 1902, the operations had absolutely no permanent or progressive effect on any symptom of the disease. Another, done two years ago, following an operation on the thyroid gland, merely to influence the persisting exophthalmos, had a directly bad effect, so that plastic operations subsequently had to be done to the more protruding eyeballs. I need, therefore, make no further reference to this method.

Let me now, first of all, speak of the danger of the operation in exophthalmic goiter, which still keeps many a patient and often his physician away from the surgeon. We have had in the last 91 operations on 63 patients not a single death, and, in the whole, we have lost only 9 patients out of 254; that is to say, 3.5 per

cent. There is no doubt that this percentage will still be lowered. If we ask why we have had a lower mortality than formerly, the answer is a very definite and short one. It is not only because of our improved technic, but because experience has shown that more prudence and care is necessary for operations in this disease than for the majority of other operations. It is not that in a greater number of cases surgical treatment has been refused, for, on the contrary, we have been able to operate in nearly all, but because we have learned to judge of the gravity of a case and to decide accordingly the extent to which the patient will stand operative measures.

Whereas, previous to my paper in 1902, extensive operations had been done (such as excision of one side and resection of a part of the other side of the gland, excision of one side together with ligation of arteries of the other, and ligation of more than two arteries in one session), in the last 100 cases such operations have merely been done exceptionally, and only when we were sure the patients could stand them. Very often we had to begin with the ligation of a single artery, and even this only after a long preparative treatment of the patient.

Let me tell you in a few words what we consider important for every surgeon to know before he attempts operations of this character. Above all, we have to investigate the strength of the heart. In the majority of cases, and especially if the disease has been of long duration or has presented sudden exacerbations, we find the heart dilated. We are then to decide whether or not we have to deal with a compensatory hypertrophy, the result of increased cardiac activity brought about by the tachycardia. If this is the case, the dilatation will be slight and constant, and, what is more important, blood pressure will be increased. This we find in the majority of cases. A systolic blood pressure, even of 195 mm. mercury (Riva Rocci), does not forbid operation, but

we must be sure that the high pressure is proportional to the degree and constancy of tachycardia. If this is not the case, extreme care is necessary. If we find the blood pressure below normal and the disease highly developed, we must study the condition and especially note the action of the heart after exertion or excitement. Under these circumstances we might find a sudden, very marked dilatation of the heart, irregularity of pulse and a blood pressure which can not be measured with our ordinary methods. These patients must be carefully watched and prepared for operation and, what is more important, they should never be submitted to an immediate extensive operation.

The second point which we have to consider is the degree of the disease at the moment we are asked to operate, and this particularly concerns the degree of intoxication presented by the patient at that moment. Intoxication is evidenced by special symptoms, such as sleeplessness, extreme nervousness, great fatigue, weakness, diarrhea, vomiting and a high degree of tachycardia, with irregular pulse and a very vascular thyroid. A highly vascular gland, with expansile pulsation—that is to say, with dilatation of the capillaries (what we call struma telangiectodes) is a sign of very severe intoxication. We find these symptoms more pronounced in the early stages, especially when there has been a rapid development of the disease. Such symptoms do not warrant an extensive operation, and the patient consequently should be prepared merely for a slight operation.

Of further importance is the examination of the blood in exophthalmic goiter, for through this we are apt to find an answer as to the gravity of the disease. Up to the present time 58 cases have been carefully examined by Dr. v. Steiger, who has done special work in hematology. In nearly all typical cases of the disease we find an increase in the number of lymphocytes and a decreased number of the polynuclear forms, the total number of leucocytes being normal or rather low. The num-

ber of lymphocytes is sometimes absolutely increased, but more often the increase is a relative one. This increase is proportional to the degree of the disease, and if there is no increase of lymphocytes the case is an especially serious one. Only in very early, undeveloped cases and in those of long standing which have improved do we find that lymphocytosis is absent. Some time after operation the numerical proportion of the different forms of leucocytes becomes either normal or nearly so, in accordance with the improvement of the patient. We know very little as yet of the significance of lymphocytosis. That form of lymphocytosis which follows infections must be regarded as a secondary hyperproduction in the lymphoid tissues, damaged by the acute infection. Lymphocytosis, on the contrary, is a primary and specific process and indicates a hyperfunction of lymphoid tissue, probably according to its want, and this can not be merely a local effect, as there is a substitution of the myeloid leucocytes at the same time.

We furthermore know very little of the function of the lymphocytes themselves. Their number is increased in slight or chronic infection, and more especially in intoxication, and we must admit that in exophthalmic goiter an analogous irritation of lymphoid tissue takes place. We know that wherever this irritation takes place lymphoid tissue can form, and it is an interesting fact that in exophthalmic goiter the lymphatic glands in the neighborhood of the thyroid are hypertrophic, and more especially lymphoid tissue and germinal centers are also present in the gland itself, which indicates that the thyroid body is the place of origin of this irritation. We find that this local formation of lymphoid tissue in the thyroid body is present also in early cases, even before there is evidence of lymphocytosis of and diminution in number of polynuclear leucocytes in the peripheral capillaries, which latter is the result of the toxic influence on the bone-marrow. After excision of a part of the gland, we also find the lymphocytes diminished,

whereas their number increases after ligation of arteries.

It may be seen by this brief statement what important results the examination of the blood may give as to the gravity of a case. The very fact of substitution of myeloid leucocytes by lymphocytes seems to me of further importance. It might explain why an ordinary, even slight infection or intoxication acts so badly on a patient with exophthalmic goiter, because ordinary leucocytosis can not get so far or substitute lymphocytosis. Therefore, the patient's condition may be very bad with a slight infection, or the symptoms of exophthalmic goiter may increase often to a dangerous extent. We found, for instance, in a patient with this disease who developed tonsillitis, only 7,000 polynuclear leucocytes and 3,400 lymphocytes, though the symptoms of infection were very marked and a very high temperature was present. The same fact of substitution might explain some of the sudden deaths after operation in severe cases, in analogy to the sudden deaths in lymphatic conditions. When the gravity of a case has been thus established, we can determine the time and decide on the method of operating, for sooner or later we will be able to operate without fear.

Now the second and more important question arises: Can we cure the disease by operation? Most surgeons have noticed an immediate increase of the symptoms after operation, which symptoms can even become fatal. I have, in my paper in 1902, claimed that this postoperative aggravation is due mostly to hemorrhage and absorption of toxic blood, especially when gland tissue is resected and injured in any way during the operation. This opinion has since been widely confirmed. By most careful avoidance of any bleeding, by ligation of every small vessel, and by taking the greatest care not to injure the parts of the gland to be left, we can avoid alarming symptoms almost completely. As a matter of fact we see such symptoms at the present day only if,

for any reason, the operation had to be done quickly and the gland tissue was injured.

When the immediate effect of the operation is over (and when it has been done under local anesthesia the disturbance lasts but a few hours), the surgeon is surprised at the striking improvement in the patient's condition. The very fact that the symptoms of the disease may disappear so soon after the operation, so that many times the patient is almost normal in a few days, seems to us to be the proof that we have touched the disease in its important place.

I think that it is generally admitted nowadays that the thyroid gland is diseased in every case of exophthalmic goiter, and it is also admitted that it shows functional alteration. It is much to the credit of American physicians that they have demonstrated what are the exact histologic changes in the thyroid gland in this disease. The proliferation of the epithelium, which assumes the cylindrical type, and the liquefaction of colloid are the most striking features and, especially when compared with the hypertrophic glands described in Halsted's classical experiments, these changes seem to furnish proof of a functional disorder. Still it has been difficult for those who have examined large series of cases and also for those who see a great deal of other diseases of the thyroid gland, to accept the above-mentioned changes as being specific for exophthalmic goiter. We find the same enlargment of follicles with formation of papillæ and high cylindrical cells, together with the decrease in thick colloid, in glands of normal size in hypertrophic as well as in nodular goiters, without the slightest symptom of exophthalmic goiter. But we find them in a part of the gland or in a nodule where vascularization is rather diminished, while the diseased parts in exophthalmic goiter, even if present in areas only, will be found in very vascular parts, as, for instance, in the periphery of the gland or a nodule. We must conclude, therefore, that the histologic changes

themselves do not account for the symptoms of the disease, but it is the change of metabolism which shows itself by the increased vascularization of these parts. Chemical experiments, which I can not discuss here, show that material, such as iodin, is taken up eagerly by the thyroid gland in patients with exophthalmic goiter and is not eliminated by the kidneys as it is in normal individuals.

Besides these histologic changes, we must consider, as characteristic for the disease, the formation of lymphoid tissue in the thyroid glands, and in special cases the presence of large cells with specially differentiated protoplasm. The diffuse infiltration with leucocytes and the desquamation of the epithelial cells, which we find very often in the inflamed gland in exophthalmic goiter and which have been described by several authors as being characteristic of the disease are secondary. This may be the result of handling and injuring the gland during operation or the result of treatment with Roentgen rays, electricity, injections, etc. We also find it regularly after ligation of arteries in previous operations.

What are we accomplishing by our operations on the thyroid gland in exophthalmic goiter? Only exceptionally a limited and well circumscribed part of the gland is diseased and can be entirely removed. It happens when the disease develops in a subject with nodular goiter and may also account for the prompter cure of these cases by operation.

Nearly always the changes are diffuse, though in areas, and it is not possible to take away all diseased tissue without depriving the patient of the thyroid function altogether. This is, in my opinion, not permissible. What we can do is to reduce the diseased tissue or its increased vascularization and thereby reduce the assimilation. It has proved that the nearer to the normal we reduce the gland, or its blood supply, the prompter the cure will be. I think it is the best proof against a

perverted secretion of the thyroid gland in exophthalmic goiter, that even when we leave behind so-called diseased gland tissue, but under normal blood supply, the improvement after the operation is immediate and goes on to entire cure. We must admit, therefore, that the so-called diseased part of the gland can assimilate normally and, more than that, it can become normal itself or rather adapted to further claims.

The fact that increased vascularization is indispensable for the development of the disease also proves that what reduces vascularization prevents its development. We easily understand, therefore, that in nodular, and especially colloid goiter, with mechanically reduced vascularization owing to the great accumulation of colloid, the disease does not easily develop, whereas it does readily in normal and slightly hypertrophic glands. Based on these facts, the operation has been carried out in 254 cases and the results are as follows:

There is not a single case of ours in which the patient has not been much benefited by the thyroid operation. We have cured by our operation the patients in 83 per cent. of all our cases. There are 73 per cent. of the patients with the so-called primary disease healed; 92 per cent. of the patients having the disease combined with ordinary goiter, and 100 per cent. of the patients with vascular goiters. Some of the observations date back 15 and 17 years since the time of observation, without recurrence of the disease, provided that the operation was carried so far that vascular symptoms of the thyroid disappeared completely. In cases of this type the patients are all completely cured, so that no symptom of exophthalmic goiter remains. But the time required for recovery has varied greatly, it being especially long before the heart and eyes became normal again. I wish especially to say that our chances of cure do not so much depend on the degree and the extent of histologic changes as on the duration and the secondary changes in the case.

We have had cases in which the excised gland showed excessive epithelial proliferation in all parts and in which the patient presented all the symptoms in the highest degree, and yet the cure has been just as complete and rapid as in patients showing much colloid matter and less severe symptoms. The difference between the two lies in the fact that the former, as a rule, not only develop very rapidly but also progress rapidly. Hence an operation must be undertaken early before organic changes take place, and also before the thyroid tissue has undergone induration—that is to say, before the excessive proliferation of cells has mechanically reduced the capillary supply and a part of the functional tissue, and also before infiltration and desquamation have destroyed a part of the functional tissue. These latter changes are the cause of symptoms of hypothyroidism.

Secondary organic changes of this nature were present in 4.8 per cent. of our cases. The patients were all very much benefited by the operation, but some heart trouble, the impossibility of much exertion and more or less exophthalmos remained. These patients might present slight symptoms of hypothyroidism, but I must say that, owing to the great care my father takes in this matter, it has been the exception to see these symptoms appear after operation.

Ten patients (4.4 per cent.) were benefited by thyroid operation, but not as much as could have been expected; some of these had symptoms of other diseases and they seemed to present a special form of the disease. But space is too limited to discuss this question. Eight patients (3 per cent.) are still under observation, the time since the operation being too short to give any definite opinion concerning them. In another group of eight cases (3 per cent.) the patients could be cured by the thyroid operation, but, being so much improved, do not wish it.

This brings us to the question, how operate? The

most important condition is *nihil nocere,* and that is why I have spoken, in the first place, of the danger of operation. We have seen that careful preliminary observation of the case makes a carefully conducted operation a possibility for almost every patient. The method has to be chosen for every case. We give the preference to repeated operations with the patient under close observation and with the help of medical treatment. More than two arteries should never be ligated in one session, because of the above-mentioned changes in the gland. To remove more than half of the gland at one sitting is dangerous, and it is difficult to say whether this is ever wanted. We find it rarely necessary to resect a part of the remaining gland after excision of one side.

The question, When are we to operate? depends not alone on the physician, but also quite as much on the patient. Often the surgeon thinks it the doctor's fault that he is consulted so late, and does not imagine what an unsettled and sick mind the patient has. It is necessary to advise people to see the doctor in the early stages of the disease. Nervousness, irritability, weakness, emaciation, sleeplessness are the early symptoms and are not sufficiently dwelt on. These patients are often regarded as cases of neurasthenia. If such patients were carefully examined by medical men, especially after exertion and before or during menstruation, characteristic, although slight, symptoms could often be made out; such as tachycardia, ocular symptoms, tremor, blood changes, and especially vascular symptoms of the gland.

On these latter symptoms treatment should be decided. Distinct vascular symptoms should at once induce surgical treatment. If they are wanting, the medical treatment, with the patient under close observation, may cure, but if it does not, or if relapses come on, vascular symptoms will develop before long and be at once noticed by the doctor and induce surgical treatment. In such cases ligation of two arteries or excision of half of the gland will cure definitely in a very short

time. If the doctor sees the patient only when the disease is at its worst, then we do not advise an immediate operation. Even ligation of one artery may be dangerous then, because of the increase of the discharge of toxic material from the gland and because in these cases the organism has not yet developed its own antitoxic reaction, the lymphocytosis. In these cases medical treatment is needed and cytotoxic serum here seems to act well. If the reaction of the organism is present, operative treatment must take place.

In cases of longer duration, great benefit can be derived by operation, but here one has to be even more careful, as we have to deal with organic changes in the heart and there is the fear of hypothyroidism. I wish to mention one fact, that in all cases of long duration, whether in the so-called primary cases or in the cases combined with ordinary goiter, always the same symptoms are evident—dilatation of the heart, excitable pulse, and exophthalmos. As to the latter symptom, which is mostly caused by the dilatation of blood vessels in the orbit, the fact that the eyeball does not go back, even when it can be pushed back easily, does not in all cases come from development of fat or connective tissue, as is generally admitted, but also from the fact that the muscles of the eyeball have been distended so much and so long that they can not contract well, if at all. It is possible that electric treatment might be of benefit.

We come now to the conclusion that operation on the thyroid gland gives the possibility of an entire cure of the disease. Whether we admit a primary irritation of the sympathetic nerve, and, therefore, an increased metabolism of the gland, or a primary increase of thyroid material and from it an irritation of the sympathetic system, or both, it amounts to the same thing so far as the thyroid operation is concerned. By reducing the hypertrophic thyroid tissue or reducing its blood supply, we reduce the possibility of too extensive reac-

tion to the primary cause and also enable the gland to adapt itself to counteract new outbreaks of primary causes which a nervous subject can easily show.

DISCUSSION

ON PAPERS OF DRS. BEEBE, MAC CALLUM, BARKER, PREBLE AND KOCHER IN THE SYMPOSIUM ON GOITER.

DR. W. S. HALSTED, Baltimore, expressed his belief in the efficacy of the serum discovered by Drs. Beebe and Rogers in some cases. He saw a series of cases in which the exhibition of the serum had been followed by relief, almost complete, of the symptoms of exophthalmic goiter. The result of the surgical treatment of exophthalmic goiter in the Johns Hopkins Clinic has been surprisingly successful. Of some ninety cases of this affection operated on by Dr. Halsted during the past fifteen years only two patients have died, and both of these in the current year. Of the two fatal cases, one weighed only 60 lbs. at the time of operation, and was losing at the rate of 3 lbs. a week while under observation. The other patient died very suddenly four days after operation, during apparent convalescence.

Speaking of the danger of surgical tetany, which, until the epoch-making discovery of Gley in 1891, was incomprehensible, Dr. Halsted said that it seems hardly credible that the loss of bodies so tiny as the parathyroids should be followed by results so disastrous. With our knowledge of the function of the parathyroid glandules comes not only the recognition of the necessity for their preservation, but more frequent occasion for operations which imperil the vitality of these bodies. Seven cases of operative tetany within the past two years in the practice of a certain great surgeon probably exceed in number all that have occurred in his practice during the quarter century preceding. The ligation of two thyroid arteries has in several instances been followed by tetany. From simultaneous ligation of the four thyroid arteries in exophthalmic goiter the danger of tetany is so great as to contraindicate this procedure. In performing unilateral thyroid lobectomy, Dr. Halsted maintained that one should not sacrifice either of the parathyroid glandules of the operated side, for tetany may follow the excision of one lobe, and indication for the removal of the other lobe may subsequently arise. The cases of tetany occurring in the practice of experienced operators are, he thought, less often due to the actual removal of the parathyroids than to interference with their circulation. For the preservation of these little glands knowledge of their blood supply as well as of their location is essential. Their situation is, in general, along the posterior border of the thyroid lobe, commonly in the course of an anastomotic channel connecting the superior and inferior arteries. They may be found

at any point from the top to the bottom of the thyroid gland, along its posterior border and posterointernal surface, and at least one is quite constantly found near the entrance into the thyroid gland of one of the branches of the inferior thyroid artery.

R. M. Evans has demonstrated that each parathyroid glandule has its own little artery, given off usually from a branch of the inferior thyroid or from the channel connecting the superior and inferior thyroid arteries; and directly or indirectly always from the last named arteries. Somewhere in the middle two-fifths of the posterior border of the thyroid gland these parathyroid glandules are ordinarily found, the superior one being rarely as high as the superior pole, and the inferior one frequently below the inferior pole of the thyroid gland.

Not infrequently it is very difficult, indeed, to avoid cutting off the blood supply of these glandules in the course of operation, for the parathyroid artery may be given off from its parent stem just as the latter is entering the thyroid gland. In such cases there is not room for the point of even the finest artery forceps or the parent stem distal to the point of origin, of the parathyroid artery. Twice Dr. Halsted found it quite impossible, for the reason just given, to save a parathyroid glandule; and on several occasions, in the course of operation he has transplanted into the thyroid gland a parathyroid body whose circulation was threatened or cut off. In dogs he has many times transplanted parthyroid glandules, into thyroid gland and spleen, occasionally as many as seven or eight of these little epithelial bodies into one spleen. After eight months of experimentation he has been unable to obtain functional proof of the success of a transplantation, although six weeks after the transplantation into the thyroid gland there was anatomic evidence of the success of the experiment. Hence he feels that at present one can not rely on transplantation of the parathyroid glandules. The main reliance in case of tetany is the injection, hypodermically, of the proteids of these bodies as prepared by Dr. S. P. Beebe.

Dr. Halsted stated that the procedure in the course of thyroid lobectomy which seems to him best to guarantee the safety of the parathyroid glands, is ligation of the branches of the thyroid arteries as far peripherally as possible, beyond the point of origin of the parathyroid arteries. The slicing of the thyroid lobe distal to the parathyroid bearing area, he said, is not to be countenanced in severe cases. This procedure, which may be resorted to in many cases of colloid and nonhypertrophic goiter, is in the exophthalmic form reserved by Dr. Halsted for operations on the second lobe, and for the special occasions when the blood supply of the parathyroid is such that ligation of the little radicle beyond the origin of the parathyroid artery, is impracticable.

DR. FRANK BILLINGS, Chicago, said that one must bear in mind that while there are patients who suffer with the typical symptoms, there are others who may be nervous, may have tachycardia, tremor, flashes of heat and cold, myasthenia with early exhaustion on either mental or physical effort who would ordinarily be classed as neurasthenics, but with the appearance of slight goiter could be classed under exophthalmic goiter. It is sometimes difficult to see where neurasthenia ends and exophthalmic goiter begins. It is, therefore, important to have the patient under observation for a considerable period of time in those cases when the diagnosis can not be readily made. There are two classes of patients: One the so-called secondary, where simple sturma has existed for an indefinite period, sometimes for years, and where for some cause there may be developed exophthalmic goiter. In the second class there has been no pre-existing knowledge of goiter and the symptoms of exophthalmic goiter develop suddenly. The morbid anatomy of the classic goiter of exophthalmic goiter is said to be that of the hypertrophic thyroid gland. Associated with this there is an increase in the secretion of the gland and hyperthyroidea results. It is known that in certain localities simple struma exist in larger numbers than in other places, and certain localities also give a larger number of exophthalmic goiters. Dr. Billings stated that there are three or four counties just north of the center in Illinois, from which a larger unmber of cases of simple goiter and exophthalmic goiter come than from other regions in the state. In one small village in Michigan eight cases of simple goiter occurred and two developed exophthalmic goiter. Dr. Billings urged that physicians individualize in the treatment. Last year he reported sixty-five cases of exophthalmic goiter before the Chicago Medical Society. Of this number three patients had been operated on, with one death during the operation. The other patients had been treated medically and three terminated fatally. The three fatal cases were acute manifestations of the disease and ran a rapid and very acute course. Of the remaining patients, all improved very materially on a rest treatment. No specific medication was given, but the rest treatment was given with an attempt to individualize as to the time to produce results. Ordinarily, he said, the rest treatment as prescribed by most physicians is not thoroughly given. The patient must have physical as well as mental rest. In one instance it may be the continuous recumbent posture; in another the recumbent posture must be changed for the sitting posture or even moderate walks taken to keep the patient in the proper mental state. In all cases the environment must be restful. The food should be nourishing and should be pushed to the full digestive and assimilative power of the individual. The icebag used intermittently over the precordia and over the goiter, galvanism through the goiter and in the direction of the pneumogastric nerve, cold salt glows and mas-

sage are important incidents in the management. Medication is of less importance, but for certain individuals small doses of opium are helpful. The hydrobromate of quinin, 5 grains, three or four times a day, is often helpful because of its effect on the vasomotor apparatus. If a rest treatment thoroughly carried out results in a decided improvement, one would be justified in continuing it. If it is not helpful to the individual or if the individual's financial conditions or relation to the family are such that it is impossible to take a rest treatment, then, Dr. Billings said, surgery is indicated. Although less objectionable than formerly, if a member of his family suffered from the disease, Dr. Billings would prefer at first to try the rest treatment rather than to at once submit to surgery. In his experience with the few patients he has seen operated on, entire recovery has not occurred, as it does not occur in those managed medically. Such patients continue to show moderate cardiovascular disturbances and more or less tremor and other evidences of neurosis.

Dr. William J. Mayo, Rochester, Minn., said that three types of these cases are seen clinically. First, the vascular type; second, the type that is due to a hypertrophy of the thyroid tissue, and third, those cases of hyperthyroidism developing in patients with pre-existing goiters. There is a fourth or pseudo-type in which there is not a true exophthalmic goiter or hyperthyroidism, but where a tumor, such as an adenoma, develops in the gland inside of the capsule and produces pressure on the gland. In other words, the tension within the capsule of the gland causes a greater amount of secretion to be absorbed. Such cases, he said, do not require removal of the thyroid, but simply removal of the tumor. Dr. Mayo considered one point brought out by Drs. Halsted and MacCallum exceedingly important in this connection, and that is, that there is practically no difference between the glandular overwork that comes from experimental removal of part of the normal thyroid gland and cases of hyperthyroidism. In other words, that there is practically no difference between a gland which has been hypertrophied as the result of necessity produced by operative removal experimentally, and those cases in which this takes place not as a result of such a necessity. These cases, then, can be shown both clinically and microscopically so plainly that there can be no question regarding their existence. Another point brought out by Dr. Barker he thought also important, and that is that some of these patients do not, apparently, have goiter. That was his opinion for a while, but he now finds that in every case, whether the goiter is apparent or not, there is enlargement of the thyroid, and that those cases with pre-existing goiter, where proper areas are cut and examined, the typical changes, macroscopic and microscopic, can be shown. As to the relief of these patients, Dr. Mayo said they can be cured by operation. A

failure to cure, as a rule, is due to failure to remove enough of the gland. In regard to the question of tetany, Dr. C. H. Mayo found in a large number of cases but one case of tetany and that was exceedingly mild and soon disappeared. Dr. Mayo said that if the posterior capsule of the thyroid is carefully preserved, and the tumor removed from above, it is impossible to cut into the parathyroid glands.

Finally, in regard to the question of operative mortality, Dr. C. H. Mayo reported 176 cases of hyperthyroidism operated on with nine deaths. There were four deaths in the first sixteen cases operated on; three in the next thirty cases, and three in the remaining cases. There was but one death in the last 75 operations. The earlier operations were done with a considerable loss of blood. They were cases in which the medical treatment had failed. They were operated on at a bad time, and the result was a high mortality. With careful preparation this is largely disappearing, and Dr. Mayo believes that one can now look on hyperthyroidism as a surgically curable disease; not in all cases, but in those turned over to the surgeon by the medical man not too late when they feel that these cases have been subjected for a reasonable length of time to medical treatment without relief. Such cases can be looked on as being susceptible to a cure by surgical means.

ABDOMINAL SYMPTOMS OF THORACIC DISEASE.

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Acute pleuritis is sometimes accompanied by pain referred to the hypochondriac region of the affected side, and a peculiarity of the pain is its constancy. It is not felt merely on deep breathing, nor more severely on inspiration, as is so commonly the case with pleuritic pain in the nipple region. Exertion and cough, however, are prone to accentuate it, and it may cause more or less grunting respiration. I recall one case of severe epigastric pain caused by diaphragmatic pleuritis in which cough was absent, and in such a case it is difficult to arrive at a diagnosis at the onset of the disease, time and developments being necessary to determine the real nature of the affection. The abdominal pain that is present in some cases of lobar penumonia, however, is particularly striking in its deceptive characteristics. Last autumn I observed two cases in which the onset of the disease was attended by extreme pain in the region of the gall bladder, indeed, cholecystic disease was seriously considered until there appeared physical signs sufficient to call attention particularly to the lower lobe of the right lung. There was no chest pain proper, but, on the contrary, the pain radiated downward from the region of the gall bladder. The disease was not ushered in by a distinct chill nor was the temperature high, and the early diagnosis was further confused by the absence of cough. The respirations were only moderately in-

creased at the beginning. One of these patients was a woman 80 years of age, and there was felt in the right hypochondrium a mass suggesting a dilated gall bladder. Her leucocytes were high, 30,000, and death ensued in a few days. The other patient was a woman of 47 years who was, and had been for ten years, practically bedridden with arthritis deformans. In her case also at the onset of the disease the liver was by palpation and percussion found abnormally below the free border of her ribs. Her leucocytosis was only 18,000 and she also died after a short illness.

Not only may the pain of lobar pneumonia be felt in the epigastrium or hypochondrium, but in rare instances it may be present in one of the inguinal regions. If in the right iliac region the disease may simulate appendicitis so closely as to render some difficulty in diagnosis. In illustration of this point I may cite a case occurring in the practice of Dr. DeLancey Rochester. He was called to see a boy, whom he found with a moderate elevation of temperature, and pain, tenderness and rigidity in the right iliac region. There was constipation, coated tongue and an absence of other symptoms ordinarily attending the onset of pneumonia. Surgical consultation was had, the boy was removed to a hospital, and a normal appendix was removed. The temperature rose, and within the following twenty-four hours the physical signs of pneumonia of the lower right lobe developed. In this instance the early absence of cough and chest signs, coupled with the distinctive manifestations of disease in the right iliac region, led to the adoption of the course related. Leucocytosis, while not often high in early appendicitis, yet reaches a figure that might well accompany pneumonia, and if a high leucocytosis were present in such a case it would not draw attention from the appendix as the seat of the disease. It must be admitted that the symptom-complex in Rochester's case would prompt most alert physicians to advise prompt operation. The case, however, em-

phasizes how distant from the seat of trouble may be an abdominal symptom in thoracic disease, and at this point it is well to call attention to the fact that with the abdominal pain there is often tenderness on pressure and either rigidity or tympanites. In all the cases above mentioned there existed more or less abdominal tenderness and rigidity, though these symptoms were less marked in the region of the gall bladder than in the region of the appendix in the case last spoken of.

Among the more acute diseases of the lungs or pleuræ that exemplify the point of my paper, none does so more strikingly than empyema. This affection may give rise to symptoms of an acute inflammatory or suppurative condition of a part below the diaphragm. In this connection we are reminded of the atypical behavior of physical signs in some cases of pulmonary disease. It has probably been observed by most of us that in some cases signs are either exaggerated, meager, absent or contradictory when viewed in the light of later developments in the case or when compared with post-mortem findings.

It happened in these cases so far recited that physical examination of the chest failed to disclose, early in the history, the nature and seat of the disease. There was a transference of the usual symptoms from the chest to the abdomen and an abeyance of the physical signs, as all the patients were carefully examined by palpation, percussion and auscultation.

The case of empyema illustrative of its possible deceptive character was seen in the Buffalo General Hospital under the care of Dr. Stockton. The patient was a young man of strong physique who entered the ward complaining of severe pain in the left side extending from the lumbar region around to the umbilical region. He had a high intermitting and remitting temperature, a heavily-coated tongue, nor were his respirations more disturbed than might have resulted from the acute abdominal pain. There was some tenderness and rigidity

of the muscles of the left side of the abdomen. On deep palpation in the region of the left kidney considerable pain was elicited. There existed some abdominal distension. The patient grew steadily worse and operation for a probable perinephritic abscess was decided on, but at that juncture physical signs of fluid in the left pleural cavity developed and the exploring needle revealed an emypema, from which the man made a timely recovery after an Estlander operation.

The explanation of the transference of pain to the abdomen in thoracic disease is clear when we recall the anatomy of the six lower intercostal nerves, branches of which are supplied to the abdominal parietes. It is notable that pain is especially felt in the abdomen in cases with acute inflammation of the parietal pleura.

To turn from pain in the abdominal regions accompanying pulmonic disease let me call attention to abdominal tympanites as a symptom in lobar pneumonia. This constitutes one of the most troublesome, annoying and unyielding symptoms of the disease. Sometimes it supervenes early in the course of the affection, but it is more often a condition occurring at the height of the disease when nervous, circulatory and muscular powers are overwhelmed by the septicemia. The abdomen is greatly distended, but is flaccid and toneless. Cathartics may reduce the distension in a slight degree, but it is apt to return promptly. High enemata sometimes diminish it, but unfortunately they frequently fail to give relief. The distension seems to be due to extreme relaxation, almost paralysis, of the muscular coat of the intestine, the diaphragm and the abdominal parietes, and not infrequently distension is so pronounced that respiration is materially interfered with, while at the same time the bowels respond readily to mild catharsis, apparently an anomalous state of affairs. In some cases tympanites encroaches on thoracic space to such a degree as to occasion or increase already existing cyanosis, and when the bloating is amenable to treatment the circula-

tion of the patient is seen to improve. This symptom is observed more especially in the extremes of life and in obese subjects with low resistance and myocardial disease. In its most aggravated form it is of ill prognostic significance and its treatment is eminently unsatisfactory. In most cases special remedies are of little or no value, while it yields only to strychnin, fresh air and general eliminative measures. As special remedies, however, physostigmin salicylate, 1/100 grain hypodermically, has seemed useful in a few of my cases, and ergot for its effect on unstriated muscle may prove advantageous. Small doses of digitalis or strophanthus, through their influence on the circulation, sometimes lessen tympanites. Carminatives that are also stimulants, such as compound tincture of cardamom, compound spirits of lavender, kümmel, oxycamphor, aromatic spirits of ammonia, etc., have given relief in some cases, while reputed intestinal antiseptics have, in my experience, proven woeful failures. A light ice-bag or ice-water coil, over the epigastrium occasionally serves to impart tone to the abdominal sympathetics.

Let us now consider abdominal symptoms as they occur in connection with cardiac disease or morbid conditions of the aorta. One of the most common is epigastric pain resulting from myocardial disease, and I may best illustrate this by the case of a woman near three score years of age, who was seized in midafternoon with intense epigastric pain accompanied by vomiting. Under suitable doses of morphin hypodermically the pain subsided and the night was spent with a fair degree of comfort. The next day epigastric pain and vomiting recurred and were again controlled by morphin. The following day the patient suddenly died, and at autopsy there was found hemopericardium with rupture of the left ventricle near the interventricular septum and the apex of the heart. We argued that the tear in the cardiac wall, which was one and a half centimeters

long, had occurred slowly and the extreme pain of the process was referred to the epigastrium.

Another case was that of a middle-aged, hard-working man from the country, who was referred to me some years ago, and who complained of stomach symptoms, chiefly gastric pain, eructation and vomiting. His heart was irregular, weak and dilated; his pulse small, weak and irregular. His blood pressure was low, as pulmonic accentuation was marked and he had considerable cyanosis. Although I wrote his physician that his gastric symptoms were due to his cardiac condition, I failed to predict a rupture of the heart. The patient returned home, was put at rest in bed, was given cathartics, iodids in small doses and strychnin, but he grew steadily worse and died a few days thereafter. His physician wrote me that he found postmortem a small rupture of the left ventricle.

Not alone in such extreme degrees of myocardial degeneration are gastric symptoms pronounced; we frequently encounter them with angina pectoris. In cases now under observation the patients complain of flatulence and periods of great gastric discomfort, and they are persistent in their opinion that most of their trouble arises from disordered digestion. In several such cases within the past few years careful examinations of the stomach have disclosed normal gastric chemistry and motility; commonly, however, the stomach by percussion and inspection is found distended with gas and pressing uncomfortably on the diaphragm. In one case of typical angina pectoris there is present a great prominence, almost protrusion, of the gastric area, tympany rising high and suggesting eventration of the diaphragm. It is to be noted also that the stomach symptoms yield not to digestants, stomachics nor gastric sedatives, but subside under the effects of iodids and nitroglycerin. Mention of these cases brings to mind a few instances of gastralgia in men who did not complain of chest pang nor of radiation of pain to the shoulders or arms, but

who experienced relief by taking iodids and nitrites. In these cases, by direct examination, by exclusion and by therapy, cardiovascular disease was diagnosticated as the cause of their so-called gastralgias.

Doubtless aortitis is the fundamental fault in not a few of such patients, as the pain caused by thoracic aortitis may be felt in the epigastrium.

In many cases of valvular heart disease with failure of compensation resulting in general venous congestion there exists troublesome epigastric distress, pressure and more or less pain which is often associated with nausea and vomiting. In some instances the passively congested liver seems the chief cause of the symptoms, and I have marked it particularly in patients with hepatic enlargement. In others, while the liver dulness is little or not at all increased, the gastric distress is pronounced, and in these patients the symptoms are to be ascribed to general portal engorgement with special gastric congestion and low grade gastritis.

An important factor also exists in the dilated and over-distended superior mesenteric vein. Possibly the abdominal gastric sensations are the result of pressure of the enlarged and heavy heart on the diaphragm; at all events we see increasing cardiac dilatation accentuate symptoms. Whatever the exact explanation of the occurrence of the symptoms, it is plain that they yield only to measures that better cardiac action and the circulation generally.

In addition to the morbid manifestations already mentioned there may result from cardiac failure more or less abdominal distension, ascites or edema of the abdominal parietes.

So also may gastrointestinal symptoms be caused by chronic pulmonary disease such as asthma and emphysema, with or without chronic bronchitis. The intimate relations existing between the digestive organs and the chest organs in asthma are familiar to us all. We are reminded of the disaster following overindulgence at

dinner by the confirmed asthmatic, and the difficulty in such cases lies not so much with the stomach as with the lungs.

From this short paper detailed discussion of causes and effects is of necessity omitted, my prime object being merely to summarize a few of the most common and important morbid conditions and symptoms that may result as above described.

This presentation is entirely clinical. Laboratory examinations were made in all the cases mentioned, but bedside observations alone were of most importance in clearing up doubtful points and arriving at correct diagnoses.

DISCUSSION.

DR. C. F. HOOVER, Cleveland, said that the subject of abdominal distress in intrathoracic disease has a very practical significance in differentiating between supraphrenic and infraphrenic disease. Five years ago he investigated all the literature on the subject in the Surgeon-General's library and was surprised to find the most comprehensive article on the subject was published by Gueneau de Mussy in the *Archives Générale de Médecine* in 1853. Mussy described the abdominal symptoms due to irritation of the phrenic nerves and described three pressure points in phrenic irritation: One directly over the phrenic trunk between the sternal and clavicular heads of the sterno-cleido-mastoid muscle, another point situated about one anda half inches external to the median line and about two inches above the level of the umbilicus, and a third point over the eleventh intercostal space or the twelfth rib slightly external to the erector spinæ muscles. In pneumonia, pleurisy and pericarditis pain in the upper abdomen is occompanied by tenderness on pressure over all these points, but the most striking sign is the supraumbilical area of tenderness to pressure which is no larger than a 10-cent piece. This point is described in French medical literature as the "bouton diaphagmatique de Mussy." In Cleveland it is commonly spoken of as "Mussy's button." In well-marked cases light pressure over Mussy's button causes pain and rapid, shallow breathing. The existence of all these signs described by Mussy does not invariably prove the case to be one of supraphrenic disease. Dr. Hoover said that several times he has seen cases of gallstones with pericholecystitis which gave all three signs as clearly as they are seen in intrathoracic disease.

DR. ALFRED STENGEL, Philadelphia, believed that Dr. Jones' paper was particularly important from the point of view of

diagnosis in those conditions in which inflammatory abdominal disease is suspected. It happened in his experience that he had several cases of pneumonia that had been regarded as appendicitis, and had been operated on. The operation revealed a normal appendix and subsequently the real condition of pneumonia rather than appendicitis was learned. The reference of the pain in thoracic disease to the abdomen is more common in children and early life than in later life. The form of abdominal disease occurring with thoracic disease, to which attention was called, is that associated with extreme tympanitis and sometimes complete intestinal paralysis. This sometimes occurs in pneumonia; it occurs more frequently, he believes, in cases of pneumonia in which there is a diaphragmatic pleurisy associated. Dr. Stengel recently had a case under observation that was dramatic and tragic. After the sixth or seventh day of pneumonia, the patient appeared to have entered the crisis and early convalescence, when there happened an enormous intestinal distension, with complete paralysis of the bowel and death. His attention was called to this a number of years ago and he had followed with great interest a number of cases since. It seemed to him that there is, in these cases, an implication of the splanchnic nerves as they pass through the diaphragm. Owing to the diaphragmatic pleurisy, by contiguity of tissue, these nerves perhaps become involved. At all events, in cases of double pneumonia, in which the diaphragmatic symptoms are associated, the occurrence of this dreaded complication has occurred, in his experience, in a number of instances; great tympany, complete intestinal paralysis, with abdominal distension, crowding the diaphragm upward, and death from that cause.

Dr. Alexander Lambert, New York, stated that in various consultations the frequency with which abdominal conditions had been diagnosticated when the trouble was in reality angina pectoris has been forcibly impressed on him. The cases in which pneumonia has been mistaken for appendicitis and in which pleurisy has caused acute abdominal pain have been very interesting. So far as his experience goes, when the pain is due either to pleurisy or to pneumonia, there is a short space of time between expiration and inspiration when the abdominal wall relaxes. The muscular rigidity, so characteristic of peritoneal involvement can be caused by pleurisy, but there is a period during which the rigidity is momentarily relaxed, when this differentiation can be made. In true appendiceal attacks there is invariably some point of abdominal tenderness; in pneumonia or pleurisy this tenderness is lacking.

Dr. W. S. Thayer, Baltimore, mentioned a case of thoracic disease with certain remarkable abdominal symptoms which he believes worth recording. Last year he saw with Dr. I. E. Atkinson of Baltimore, a man who had been under Dr. Atkinson's care for some years suffering from epilepsy. The patient

was 52 years old and had had these attacks for two years at intervals of several months. He was an excessively nervous man, irritable, querulous and difficult, full of fears and fancies. One day he sent for his physician, complaining of excruciating pain in his chest; this began apparently with a sharp pain about opposite the third left intercostal space. When seen he seemed to be suffering greatly, but could not definitely localize the pain. For the following day he was in bed, complaining of pain now at one point, now at another, now in his back, now throughout his chest. He seemed to be in great suffering, but was kept reasonably comfortable by two hypodermic injections of one-fourth grain of morphia. Dr. Thayer saw him on the following day, and again two days later. During that time he was very irritable and nervous, complaining of the same indefinite pain. He asserted constantly that he was in agony and feared impending death. On careful examination a few crackling râles were heard in the lower left axilla which might have been a slight pleural rub or simply the expansion of the atelectatic lung. On the fourth day there was also noticed a slight dulness at the right base, with enfeeblement of respiration and a slightly nasal character of the voice sounds. The abdomen was slightly distended and a little tender, especially in the region of the appendix. The leucocytes were 18,000. He remained in about the same condition until the morning of the seventh day, when he suddenly collapsed. Dr. Atkinson found the patient with a gray, peritoneal facies; pulse ranging from 120 to 130; abdomen excessively distended; temperature from 101 to 102 F. Dr. Halsted operated shortly afterward. The patient became pulseless and nearly died on the table. On opening the abdomen the colon was found to be enormously distended, so much so that the case was regarded as one of obstruction. No exploration could be made. The colon was opened and the distension immediately relieved. The patient seemed actually to come to life again. The distension of the colon was so great that the peritoneal coat was ruptured at the point exposed. The man died two days after the operation. Necropsy showed a dissecting aneurism beginning at the end of the arch of the aorta. Its onset had caused the intense pain in the chest. It had burrowed downward and there had been some escape of blood into the base of the right pleural cavity, which had accounted for the dulness on percussion and the nasal voice sounds. It had extended through the diaphragm into the region of the celiac axis, resulting in a paralytic ileus. The distension of the colon was so great that the peritoneal coat was torn in several places. The great distension of the colon stopped rather sharply at the splenic flexure without apparent cause. Dr. Thayer mentioned this case because of its remarkable characters and because of the fact that it was, after all, an in-

stance of abdominal symptoms depending primarily on a thoracic change.

DR. W. H. NEILSON, Milwaukee, said that he is especially interested in Dr. Hoover's remarks regarding the points of tenderness because hitherto he has been obliged to wait until the development of symptoms other than those referred to. He has had a number of cases in which the first symptoms are abdominal, some simulating gastritis and some appendicitis. In all the cases, if he waited a few days, thoracic symptoms showed themselves. A few weeks ago he was called in consultation to see a woman with symptoms similar to those described by Dr. Thayer, restlessness, slight elevation of temperature, with trouble of several months' duration, variously diagnosed. He found the heart with a galloping rhythm, pulse unequal at the two wrists, and the patient complained of pain over the sternum, stomach and colon. He could detect no bruit. A diagnosis of aortitis was made. The pain was arrested only by the use of morphin. About three weeks later he was again called in and found the patient in a comatose condition and with hemiplegia.

DR. ALLEN A. JONES, Buffalo, said that the points made by Dr. Hoover are very valuable in certain cases, but there are cases in which they will be lacking. He referred to the points of tenderness along the distribution of the phrenic nerve. The abdominal symptoms are often pronounced in thoracic disease, especially in children. Dr. Jones did not make the same observation as did Dr. Lambert, regarding abdominal rigidity in cases of pneumonia. On the other hand, in his paper Dr. Jones speaks of the flaccid condition of the abdominal walls. Dr. Jones said that Dr. Lambert's statement regarding the period of relaxation of the rectus muscle is of value and he will watch for it in the future. Dr. Jones had referred in his paper to the cases of appendicitis being closely simulated by pneumonia. Dr. Thayer's report illustrated splendidly, he said, the unreliable character of abdominal pain as a symptom. In many cases it is most misleading and keeps one guessing at all sorts of diagnoses. His report is valuable in corroborating what was stated regarding aortic disease occurring with abdominal symptoms.

A CLINICAL STUDY OF BLOOD PRESSURE VARIATIONS IN DIABETES AND THEIR BEARING ON THE CARDIAC COMPLICATIONS.

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The pathologic conditions of the circulation in diabetes and their bearing on the prognosis of that disease have been made a subject for publication by a number of observers, including Jaques Mayer, O. Israel, Schott, von Schmitz, Ebstein and Leonard Weber. My purpose in reopening the subject for discussion is to consider the question from the vascular standpoint and to submit certain observations on blood pressure in diabetes which I have conducted, covering a period of two years.

Reports differ widely as to the condition of the heart in diabetes. There are undoubtedly many cases in which the heart is normal or where the state of the organ corresponds to the general nutritive condition. It would be an amazing exception to the rule of toxic degenerations if the circulatory system could withstand without detriment the irritation of so prolonged and in many cases so intense a toxemia as characterizes this disease, and consequently it is not surprising that in a considerable percentage of cases some degree of cardio-vascular impairment is discoverable.

Saunby states that in 40 per cent. of his cases the heart was free from noticeable changes. In about an equal proportion it was found to be pale and soft, and in 13 per cent. enlarged. O. Israel found cardiac en-

largement in 10 per cent. of cases observed. J. Mayer records an average of 21.6 per cent. of cardiac enlargements in his first series and 27 per cent. in his second series. Virchow's autopsy reports yield a total of 13 per cent. cardiac enlargements. The average for these assembled statistics is 17 per cent. cardiac hypertrophy in diabetes. No accurate particulars are forthcoming regarding the age of patients and duration of the disease. Some degree of renal change was a pretty constant accompaniment. In the severe toxic forms of diabetes the renal condition is either a functional hypertrophy or hyaline degeneration of the tubular epithelium. In the chronic milder type of cases the renal alterations are frequently of the nature of chronic nephritis.

In rapid progressive forms of diabetes occurring in young, spare individuals cardiac hypertrophy is seldom encountered, the myocardial changes being fatty rather than hyperplasic. The histologic changes in the heart wall in this type of case are neither pronounced nor definite. The myocardium may be pale and soft, or more rarely show marked fatty changes, with brown atrophy. Glycogen granules have been found between the muscle fibers (Frerichs). Degenerative conditions of the myocardium are probably much more rarely detected during life than after death, unless attention is called to their existence by pronounced symptoms. The acid intoxication and emaciation of inveterate forms of diabetes produce grave cardiac under-nutrition, with enfeeblement of the organ. The supreme result of this cardiac weakness was pointed out by von Schmitz, who described a condition of collapse or syncope from asystole, characterized by a very rapid, weak pulse, cold extremities, but without the peculiar panting respiration which marks true diabetic coma.

In seeking an explanation for the frequent existence of cardiac impairment in diabetes the state of the circulation is of the first importance. The introduction of methods for the clinical estimation of blood pressure

furnishes us with the means for determining whether or not this factor is of importance in producing secondary cardiac defects in diabetes in somewhat the same manner as in other chronic intoxications. Very little light has as yet been thrown on this question. Such information as is forthcoming from a study of the literature consists mainly in dogmatic assertion unsupported by adequate statistics. Potain[1] stated in 1902 that the blood pressure is notably high in diabetes, surpassing even that observed in Bright's disease. This statement has found wide currency. Tiessier[2] states that in his opinion diabetes is one of the three great hypertensive diseases, classing it in this regard with aortic insufficiency and interstitial nephritis. He qualifies this sweeping statement by excluding the type of lean diabetes, that is so often complicated with pulmonary tuberculosis, in which he states we may observe hypotension instead of hypertension. Vaquez[3] reports that he had never found an elevated arterial tension in diabetes. Ott[4] reports observations on two cases, one with systolic pressure of 225 mm. in an old man with albuminuria and glycosuria; a second in a man of 40 with 6 per cent. of sugar, having a systolic blood pressure of 105 mm. Hensen includes in his records[5] two cases of diabetes with hypotension. Janeway[6] states that he has seen both high and low blood pressure in diabetes, the latter in severe cases, with marked emaciation and diacetic acid in the urine, the former, especially in the milder forms of the disease, in stout, elderly people, where chronic nephritis or arteriosclerosis existed.

The foregoing statements and observations practically cover the question as it stands to-day. It is apparent

1. La pression arterielle de l'homme à l'etat normal et pathologique, Paris, 1902.
2. Gazette des Hôpitaux, Nov. 8, 1904, 1243.
3. Gazette des Hôpitaux, Nov. 3, 1904, 1221.
4. Montreal Med. Jour., November, 1902.
5. Deutsche Archiv. f. Klin. Med., 1900, lxvii.
6. The Clinical Study of Blood Pressure, 1904, 236.

that they do not furnish an adequate basis on which to judge the matter, for besides lacking support from statistical observations, they are conflicting in character and leave the question in all essentials an open one. The observations submitted herewith are offered as a contribution toward its more accurate solution.

TABLE OF DATA OF DIABETIC PATIENTS.

Number	Sex	Age	Body Weight Pounds.	Maximum Glycosuria per ct.	Acetone Bodies	Albuminuria	Maximum Systolic Blood Pressure mm.	Minimum Systolic Blood Pressure mm.	Average Systolic Blood Pressure mm.	Complications
1	F.	21	134	1.66	0	0	120	108	114	
2	F.	46	113	4.	0	0	140	130	137	Gallstones.
3	F.	54	185	3.33	0	0	140	—.	140	
4	M.	28	130	4.	+	+	105	95	100	Alcoholism.
5	M.	46	122	3.33	+	+	125	85	100	Carbuncle, neuritis, one attack of epilepsia acetonica; Death in coma.
6	M.	56	176	2.75	0	+	156	135	147	Arteriosclerosis, myocarditis, cerebral thrombosis.
7	M.	24	136	4.	+	+	105	80	95	
8	F.	71	186	1.66	0	0	150	145	147	Arteriosclerosis,card. hypertrophy.
9	F.	50	152	2.	0	0	125	120	122	
10	F.	56	195	6.66	0	+	228	200.	210	Chron. nephr., card. hypertrophy, hemor. retinitis, gallstone.
11	M.	56	205	1.	0	0	115	115	115	
12	M.	48	207	2.50	0	0	125	120	122	
13	M.	36	135	5.	+	+	110	90	100	Death in coma.
14	M.	29	133	3.75	+	0	102	100	100	
15	F.	35	149	3.	+	0	115	105	110	
16	F.	55	137	3.	0	+	165	140	150	Chron. neph., card. hypertrophy.
17	M.	54	160	3.	0	+	165	130	145	Chron. neph., retinitis, double mitral lesion. Graves' dis.
18	M.	60	185	1.33	0	0	145	140	142	Arteriosclerosis.
19	M.	76	210	1.66	+	+	173	165	170	Arteriosclerosis, myocarditis, one attack card. syncope.
20	F.	75	160	3.	0	0	140	140	140	Gallstones.
21	F.	21	107	3.	+	0	125	105	115	Graves' disease.
22	M.	13	76	5.	+	0	90	...	90	
23	F.	26	115	4.	+	+	125	80	95	Death in coma. Sister of patient 13.
24	F.	56	150	2.	0	0	170	165	168	Uterine fibroids. Operation.
25	M.	46	237	2.50	0	0	110	105	107	Chron. appendicitis. Slight pyrexia.

My observations cover a series of twenty-five cases of diabetes of different types, at all ages, taking them as

they came under treatment for the disease. The majority of the cases were observed in private practice, a few in hospital and dispensary work. The instruments employed were Stanton's sphygmomanometer, with a 12 cm. arm-band for office readings, and Cook's modification of the Riva Rocci instrument, with 9 cm. arm-band, for bedside observations. A total of one hundred and fifty observations was made. In all of the cases except two (Nos. 3 and 22), numerous readings were taken. In many of the cases, especially those of the severe type, it was found exceedingly difficult to secure satisfactory estimations of diastolic pressure with the instruments employed, and for this reason only the records of systolic pressure are included in the table submitted:

SUMMARY OF BLOOD PRESSURE RECORDS.

Number of cases observed	25
Males	13
Females	12
Average age of patients	45
Average weight of patients (pounds)	156
Average systolic blood pressure (mm.)	127

Age is the most important factor in influencing the type of diabetes. It is well known that the disease is less severe and progressive in the stout and elderly than in young, spare individuals. The age of 50 years often proves to be the deciding factor between the severe toxic form of the disease and the chronic mild type. In the series under consideration thirteen patients were under 50 and twelve over that age. The average blood pressure of the former was 107 mm. and of the latter 150 mm. Their average weight was 138 for those under 50 years and 175 for those over that age. Age and weight are consequently seen to exert a marked influence in determining the degree of blood pressure. Acid intoxication (diaceturia) was observed in nine of the thirteen cases under 50 years of age and in only one of those over 50. The intensity of the glycosuria was apparently without effect in increasing the degree of blood pressure. Fifteen of the series observed presented a maximum gly-

cosuria of over 3 per cent. The average blood pressure in these cases was 121 mm. In the remaining ten cases the blood pressure averaged 135 mm.

If we are justified in drawing any conclusion from these figures, it is that an inverse rather than a direct ratio exists between the degree of glycosuria and height of blood pressure. This is really no more than we might expect, in view of the fact that the milder types of diabetes are observed in elderly people who are apt to have arteriosclerosis and in consequence higher average arterial pressures.

Perhaps the most interesting point involved in the present inquiry is the effect of the acid intoxication of diabetes on the blood pressure. In my series there are ten cases which developed acetonuria and diaceturia. The toxemia proved to be permanent in all cases except one (No. 19), although it fluctuated considerably in intensity from time to time.

Number of cases with acid intoxication	10
Average age	33
Average weight	131
Average systolic blood pressure (mm.)	107
Number of cases without acid intoxication	15
Average age	53
Average weight	172
Average systolic blood pressure (mm.)	140

The marked difference in the average values between patients with and without acid intoxication and the apparent disposition to hypotension in the former type of cases suggests a direct depressive influence on the circulation, exerted by the acid toxins in diabetes. Before ascribing any such influence the matter is to be examined further. These patients are invariably asthenic in type and display the general causes of low pressure, i. e., emaciation, malnutrition, mental depression, which produce subnormal values in tuberculosis and the cachectic states generally. To these factors rather than to the acid toxins direct I believe are to be attributed the falling blood pressure curve.

I cite a condensed abstract of weight, pulse, blood pressure and urine records of two cases carefully observed:

CASE 7.—Age 24. Diabetes first discovered in August, 1905.

				Urine	
Date.	Weight.	Pulse.	Blood. pressure, mm.	Glycosuria, per cent.	Acetone. Bodies.
Feb. 3, 1906.....	136	78	104	3.33	Absent.
Feb. 6, 1906.....	138	76	105	...	Absent.
Feb. 13, 1906.....	143	72	90	2.50	Traces.
Feb. 21, 1906.....	141	78	100	2.	Traces.
Feb. 24, 1906.....	143	66	90	1.66	Absent.
Feb. 28, 1906.....	141	72	108	2.25	Absent.
Feb. 20, 1907.....	138	63	80	4.	Marked.
Feb. 25, 1907.....	138	70	95	2.85	Marked.
March 1, 1907...	135	78	100	2.50	Marked.
March 4, 1907...	135	80	88	1.50	Marked.
March 6. 1907...	133	80	80	3.	Marked.

In the year elapsing between Feb. 28, 1906, and Feb. 10, 1907, I am informed by patient's family physician, he was free from acid intoxication, and remained in fair activity, following his occupation.

CASE 5.—Age 46. Disease first discovered October, 1905.

				Urine	
Date.	Weight.	Pulse.	Blood. pressure, mm.	Glycosuria, per cent.	Acetone. Bodies.
Jan. 8, 1906.....	122	90	125	3.33	Traces.
Feb. 10, 1906....	116	90	120	2.	Traces.
Feb. 26, 1906....	121	90	120	1.25	Traces.
March 12, 1906..	120	78	120	1.66	Traces.
March 19, 1906..	122	96	110	2.50	Traces.
April 2, 1906...	121	90	105	1.21	Moderate.
April 23, 1906...	121	84	110	2.	Moderate.
May 7, 1906....	121	90	120	2.	Moderate.
May 24, 1906....	121	78	112	2.	Moderate.
June 10, 1906....	120	72	100	1.66	Moderate.
July 12, 1906....	118	84	110	2.	Marked.
Oct. 9, 1906.....	114	76	110	2.	Marked.
Nov. 8, 1906...	114	78	120	2.50	Marked.
Nov. 29, 1906....	110	90	120	2.	Marked.
Dec. 10, 1906....	110	90	100	2.50	Marked.
Jan. 8, 1907.....	110	90	110	2.66	Marked.
March 13, 1907..	100	90	105	3.	Intense.
May 21, 1907....	?	96	100	3.	Intense.
June, 1, 1907....	Death in coma.				

If these records are carefully examined it will be found that while undoubtedly the blood pressure falls progressively during the stage of acid toxemia, it does so in association with a falling weight curve and increasing weakness—evidences of malnutrition which underlie hypotension in chronic nutritive diseases gen-

erally. I agree with Janeway in thinking that the progressive emaciation and cardiac weakness cause the hypotension in severe cases of diabetes rather than the acid intoxication *per se*. The point is difficult to determine and perhaps not essentially important, inasmuch as the acid intoxication and malnutrition of inveterate diabetes run hand in hand.

In the tabulated record a note is made of the various complications found in many of the cases. It is of importance to appraise the influence of these various factors on the blood pressure record. In a certain number of cases chronic albuminuria was present, unassociated with diaceturia. These cases number five in all, only one of them displaying a slight and transient diaceturia (No. 19). Without exception these five cases gave definite clinical indications of arteriosclerosis or chronic nephritis. The average blood pressure was 164 mm. In five other cases albuminuria developed in small amount late in the disease, associated with prolonged intense diaceturia (acidosis). In these cases the average systolic blood pressure was 98 mm. This observation would indicate that albuminuria occurring as a result of toxic irritation of the kidneys from acid toxins in the urine and hyperfunction has no effect in increasing the blood pressure. The high blood pressure value of the first group is attributable to the complications causing the albuminuria (arteriosclerosis, chronic nephritis). The only high blood pressures observed in the series herewith reported, with one exception, were noted in association with arteriosclerosis and chronic nephritis. Four cases (Nos. 6, 8, 18, 19) having marked arteriosclerotic manifestations gave average pressure values of 151 mm. Three cases (Nos. 10, 16, 17) complicated with chronic nephritis averaged 168 mm. One patient with uterine fibroids had a systolic blood pressure of 168 mm.

Nowhere in these records do we find the excessive hypertension declared by Potain and Tiessier to characterize diabetes. The only case displaying excessive pres-

sure is Case 10, a female with chronic diabetes association with gallstones and chronic interstitial nephritis. The high blood pressure in this instance is fully accounted for by the complications. Indeed, if we are to accept the indications of this investigation, complications are the only factors making for high pressures in diabetes, and especially is this true of arteriosclerosis and chronic nephritis, both of which are hypertensive diseases. The average systolic blood pressure of cases with arteriosclerosis was 151 mm., and of those with chronic nephritis was 168 mm. After deducting from the series reported the cases complicated with arteriosclerosis and chronic nephritis, we find the average systolic blood pressure of the remaining eighteen to be 115 mm.—a normal average. It is well known that a strong predisposition exists in chronic forms of diabetes to the development of arteriosclerosis. The frequent association of the gouty and obese diatheses with this class of cases may help to explain this tendency to degenerative arterial change. Obesity or gout pre-existing for years before the development of diabetes may carry the individual well along the road to cardiovascular degeneration before glycosuria is discovered. In some cases there undoubtedly coexists the causes of cardiac hypertrophy from associated chronic nephritis—a not infrequent complication.

Albuminuria associated with diabetes, when due to chronic nephritis or renal sclerosis, shows increased pressure values, although toxic albuminuria due to the acid intoxication of diabetes exerts no such influence. There is nothing to show that myocardial and vascular degenerations of the chronic type of diabetes are essential to that disease. All the evidence points to the fact that the complications, especially arteriosclerosis and chronic nephritis, bring about the cardiovascular secondaries. The cardiac hypertrophy noted by pathologists is attributable to these causes and not to the diabetes *per se*.

In the severe progressive forms of diabetes met with

most frequently in young, spare individuals arteriosclerosis and cardiac hypertrophy are not frequent or prominent developments. We have seen that the cardiac condition is one of enfeeblement, the myocardial changes being fatty rather than hyperplasic. Marked hypotension characterizes the arterial condition in this form of diabetes—as low reading as 80 mm. being obtained.

These patients are invariably asthenic, emaciated and depressed, and there is much reason to believe that general adynamia rather than special toxic influences are at work to produce the falling blood pressure values of severe cases of this type. The cardiac condition is a progressive exhaustion, eventuating in certain cases in cardiac collapse. The enfeeblement of the organ under these circumstances merely constitutes a part of the general denutrition and weakness. From this standpoint the myocardial changes and "cardiac collapse" described by von Schmitz in inveterate cases of diabetes can hardly be viewed as essential diabetic phenomena, inasmuch as we encounter very similar changes and a like mode of death in other severe exhausting diseases, such, for instance, as pernicious anemia and pulmonary tuberculosis. The attempt to establish the existence of certain cardiac conditions peculiar to diabetes—in other words, a "diabetic heart," has on examination little justification. None of the evidence forthcoming from an investigation of blood pressure conditions in this disease lends itself to such a theory.

The blood pressure observations submitted herewith furnish positive confirmation of the opinion expressed by Janeway in his excellent book[6] that "The disease of itself is without influence on arterial pressure; the occurrence of chronic nephritis or arteriosclerosis or angiosclerosis as a complication explains the hypertension, and the resultant emaciation and brown atrophy or fatty change in the heart causes the hypotension in severe cases."

DISCUSSION.

DR. H. S. STARK, New York, said that he believes that in attempting to establish a relationship between cardiac, vascular or muscular disease, or in fact, any form of disease, and diabetes, one is confronted by the fact that the pathogenesis of the latter disease is not known. In consequence, our conclusions of to-day, however firm they may be, may be overthrown by the discoveries of to-morrow. Therefore, in order to establish a relationship between cardiac or vascular disease and diabetes, certain prominent features of diabetes, namely, glycosuria, acetonuria and ammonuria, should be taken into consideration. Unless this is done, attempts to establish a relationship between the two diseases will fail. The *modus operandi* by which lesions of the heart or organs may be produced is by foreign bodies which act as chemical irritants. The best proof of this is seen in arterioclerosis. This in turn may cause thrombosis or embolism. Another method by which cardiac disease may be brought about is by over-activity of an organ which may make a vicious circle with other organs of the body. In diabetes, the kidney is over-worked because of the polyuria, which, in turn, is caused by the polydipsia. He does not believe it can be demonstrated that diabetic endocarditis is a distinct pathologic entity. His observation has shown him that the most frequent vascular change met in diabetes is arteriosclerosis, and the least frequent is endocarditis. One thing of importance must be remembered—diabetes, almost from the start in the majority of the cases, is a chronic affection. It may exist ten or twenty years, and necessarily it must manifest itself in almost every organ in the body. He did not believe it could as yet be established that there is such a distinct pathologic entity as "diabetic endocarditis." It always had seemed strange to him, in observing a large number of cases, why the most frequently encountered cardiac disease, namely, chronic endocarditis, should be the least frequently encountered in diabetes. It stands to reason that if there is a distinct toxic element it would first manifest itself on the valves of the heart.

DR. HEINRICH STERN, New York, expressed the opinion that cardiac and vascular changes are never the result of the diabetic state, but are produced independently or antedate the diabetic condition, and may thus (by interfering with the activity of certain glands) be at its foundation, or, finally, cardiac and vascular changes may be sister affections of diabetes; that is, the same causes may give rise to the two sets of pathologic phenomena. He reasons thus from the fact that cardiovascular changes are found only, as a rule, in diabetics of advanced age, who are affected with rather mild diabetes. In young diabetics—in spite of the occurrence of severe diabetes—cardiovascular degenerative processes are rare. Dr.

Stern said that he did not think it a justifiable procedure to attribute the cause of eventual cardiovascular disease to hypothetical toxins, to substances presumably circulating in the blood stream, but whose existence therein has never been definitely proved. He thinks it decidedly far-fetched to ascribe to the so-called acidosis all the concomitants of the diabetic affection. That very acidosis is merely a hypothetical assumption. Scientific and conclusive proof of its possibility has yet to forthcome. The existence in the urine of the so-called acetone-bodies, of acetone, of aceto-acetic acid and of beta-oxybutyric acid does by no means imply that they occur in the blood in large enough amounts to be of any account. The higher the diabetic state, the older the patient, the more pronounced cardiovascular changes; the more severe the diabetic condition, the younger the patient, the less frequent and the milder the cardiovascular accompaniments.

THE VENOUS PULSE.

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As a result of long clinical observation and application to the known physiology of the circulation James Mackenzie published in 1902 the "Study of the Pulse." This marked a new era in the study of cardiac diseases, by his practical manner of discriminating between the pathologic alterations of the fundamental properties of heart muscle (rhythmicity, excitability, conductivity, contractility and tonicity) first demonstrated by Gaskell and subsequently in greater detail by Englemann and his pupils.

Mackenzie's results depended for the most part on a careful analysis and comparison of the venous and arterial pulses, the former giving the auricular time, the latter the ventricular, and the main features of his interpretation have been accepted without any question.

In spite of the ingenious methods adopted by him, however, there may be still some doubt as to whether the features of the jugular pulse really correspond to the phases of the cardiac cycle to which he ascribes them, especially as the jugular pulse has seldom been the subject of experimental investigation, by which alone such questions can be decided.

Before taking up the clinical analysis of the jugular pulse we therefore determined to acquaint ourselves with

its features in animals, in which the actual movements of the heart can be recorded with an exactness impossible in man.

After attempting to record the venous pulse by several other methods we have found that that used clinically gives the tracing most satisfactorily and easily. A funnel was used therefore as a receiver over the jugular vein where pulsations were visible in the necks of dogs, the skin having been shaved previously. The waves were transmitted by air in tubing connecting it with a very sensitive tambour, the writing point of its lever in contact with the smoked paper of a kymograph. The carotid pulse was registered by means of a cannula in the carotid connected to a Hurthle's sphygmomanometer. The relation of the waves in the venous pulse to the occurrences in the cardiac cycle was obtained by taking simultaneous tracings from the exposed auricle and ventricle.

In order that the heart might retain as nearly as possible its normal position supported by the pericardium and the anterior mediastinal folds, the sternum was not disturbed, but a window was made in the left pleural cavity by removing two or three inches of the third, fourth and fifth ribs. Small apertures were made in the pericardium and through these stitches were taken in the auricle and ventricle and the thread from each attached to the membrane of the tambour, which connected with another writing on the kymograph.

The animals were anesthetised with morphin and paraldehyd; a tracheotomy tube had been inserted for artificial respiration. The time was recorded in fifths of seconds by Jacquet's chronometer.

In a number of experiments the venous pulse taken before and after opening the thorax was found unchanged by the operation. In all the animals examined a good venous pulse was found.

In the jugular tracing, as a rule, a series of elevations separated by deep depressions is seen. The elevations

are composed of three minor waves, which have been marked *a, c, v,* after Mackenzie's method (Fig. 1).

One of the waves (*a*) has always been ascribed by Mackenzie to the auricular contraction, and we find in our tracing that on projecting the auricular tracing on the jugular the middle wave corresponds exactly in its commencement and fall with the auricular contraction and relaxation.

The succeeding wave *c* resembles *a* closely in appearance as a general rule, and in our tracings begins with the commencement of ventricular systole and reaches its apex soon after the ventricle has reached its full contraction. It then begins to fall and its further course is obscured by its fusion with the next phase of negative

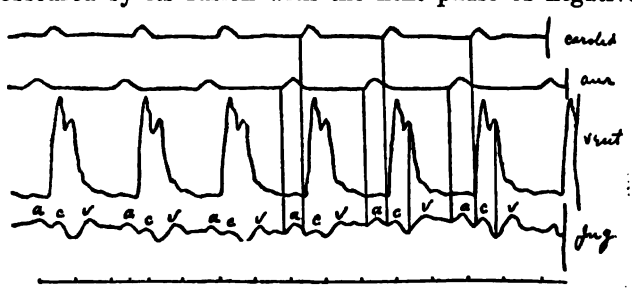

Figure 1.

pressure. The exact causation of this wave is disputed. According to Mackenzie the *c* wave is due to the pulse of the carotid artery underlying the vein being transmitted directly to the vein. Others have supposed that the wave arose from the aorta and large arteries in the thorax stiffening in the beginning of the systolic outflow and imparting the wave to the veins above them. Morrow[1] has recently revived Potain's views that this wave is produced in the interior of the heart by the ventricle in systole and is transmitted along the course of the vein to the recording instrument.

Our results point toward the view that *c* is not a simple carotid wave propagated through the vein, for it is

1. British Med. Jour., 1906, p. 1807.

often present when the jugular pulse is recorded by a method which does not involve pressure over the carotid. Thus in a number of experiments the vein was exposed and the thread of a tambour was attached to it by means of a stitch through the adventitia. The vein is thus drawn away from the carotid rather than pressed against it as in the ordinary clinical method of registration, yet a distinct *c* wave could be made out and this persisted even when the vein was dissected free from the underlying tissues, and was separated from them by the handle of a scalpel. The *c* wave, then, we regard not as a wave directly transmitted from the underlying carotid but as arising within the thorax. It occurs when the thorax is opened and thus is not due to any change in the general intrathoracic pressure.

We are disposed to regard the *c* wave as not of local origin in the neck, but are unable to decide whether it arises in the heart or in its immediate neighborhood. The question, while of interest in relation to the physiology of the heart, hardly seems to be of importance in regard to the clinical use of the method of recording the jugular pulse.

After *c* a deep depression follows, often much better marked than in Figure 1. This phase of negative pressure following immediately on *c*, the exact point of its commencement, can not be accurately determined, but the lowest point occurs about the time when the ventricle begins to relax at the end of its systolic plateau. The auricle has reached its full diastole before the apex of *c* is reached, and during the negative phase remains passive. The period along with that occupied by *c* thus represents the free inflow of blood from the veins into the auricle.

The next part of the venous pulse following on the phase of negative pressure shows some variations in appearance. Very often there is a slight rise of the lever soon tapering off into a horizontal line slightly above the level of the lowest point. This is unquestionably due to

the pressure in the veins rising as the auricle becomes filled and the current is checked. But this often is absent or little marked, the phase of negative pressure being immediately followed by a well-defined wave which has been indicated by the letter *v*. This reaches its highest point as the ventricle becomes fully relaxed and begins its phase of rest in complete dilatation. The wave after the decline of *v* until it rises again in *a*.
then slowly declines and may be followed by a very feeble oscillation before *a* commences the cycle again. In most cases, however, the lever shows no movement

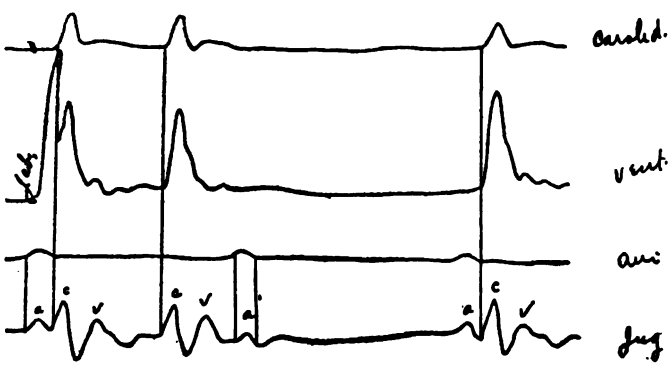

Figure 2.

The explanation of *v* has been a matter of some dispute, some holding that it is merely the wave of stasis following on the checking of the inflow as the heart becomes distended with blood. There seem to be unanswerable arguments against this explanation, however. In the first place *v* is often preceded by a distinct stasis wave which is separated from the true *v* by a short phase in which the tracing runs horizontal or rises very slowly. This stasis wave is quite insignificant in size compared with *v*.

Next, *v* always occupies a distinct relation to the ventricular movement and is entirely absent when the auricle contracts without the ventricle. This is well shown in Figure 3, in which the vagus had been stimu-

lated and the impulse of the first auricular contraction failed to pass the block and arouse the ventricle to activity. Here the *a* wave in the jugular tracing is followed by a deep depression, comparable to that ordinarily occurring, but no *v* is to be made out.

In the next cycle analogous conditions apparently prevail, the heart not yet having recovered from the inhibition, but here the impulse passes the block, the ventricle contracts, *c* appears in the jugular tracing and is followed at the ordinary interval by a well-marked *v*. It is to be noted that the phase of negative pressure is approximately equally well marked in these two cycles.

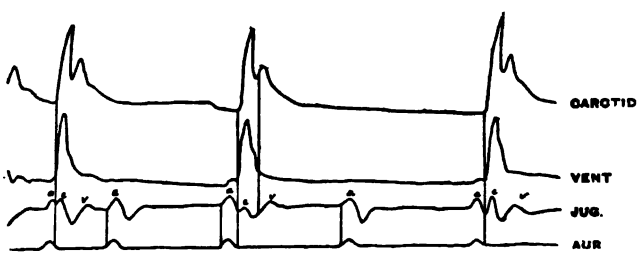

Figure 3.

In several other experiments the same results followed when the ventricle failed to contract; *c* was absent in the jugular pulse and also *v*.

On the other hand, in a certain number of cases the heart was arrested by vagus stimulation and the ventricle was excited to contract by mechanical or electrical stimuli. Here the auricle remained passive or in some cases an auricular contraction followed the ventricular (Fig. 2). Here the ventricular contraction in the second cycle is indicated in the jugular pulse by a large *c* followed by a deep depression and then by a very marked *v*. After a short pause an auricular contraction occurs and in the jugular pulse *a* may be made out followed by a depression and then by a slow oscillation.

The third cycle is introduced by an auricular contraction which leads to a ventricular systole and in the jug-

ular pulse *a, c, v* may be made out followed by a pause and then a slow oscillation which continues for some time and may have been mechanical in origin. In Figure 4 the vagus stimulation arrested the auricle completely, while the ventricle was aroused to contraction by a series of shocks. The jugular tracing presents a series of well-marked *c* waves and *v* also may be identified, though less clearly than in many other tracings.

The *v* wave thus appears to be dependent on the occurrence of ventricular systole in the dog. And the same holds true in man, for in the numerous tracings in cases of complete or partial block when an auricular contraction occurs alone no *v* appears in the jugular

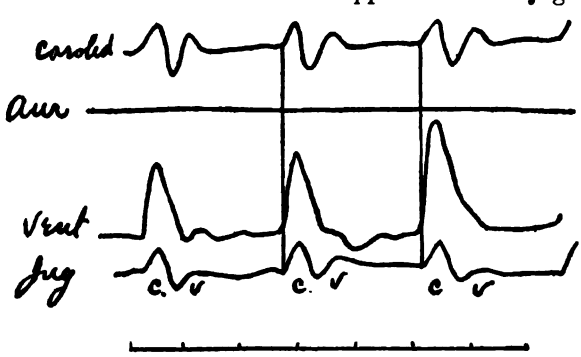

Figure 4.

pulse, but when a ventricular beat is indicated in the radial pulse the corresponding *c* and *v* can generally be found in the jugular in a case of heart block (Fig. 10).

Occasionally in the dog we have failed to observe the *v* when the rate of the pulse was very rapid, but as soon as the pulse became slower the *v* became quite evident.

The *v* wave therefore, is not due to stasis, but our experiments do not suggest in themselves a satisfactory explanation. Some light has been thrown on the subject by the investigations of Keith,[2] who showed that the points at which the superior and inferior venæ cavæ

2. Lancet, Aug. 11, 1906, p. 631.

pierce the pericardium serve as fulcra on which the musculature of the heart acts, through the attachment of the pericardium to the cervical fascia above and the central tendon of the diaphragm below. He supposes that when the auricles contract the auriculoventricular septum is pulled upward and the following ventricular contraction lowers it again, thereby assisting in filling the auricle. On this view the relaxation of the ventricle might be supposed to exercise the reverse effect on the auricle and cause an increase in the intra-auricular pressure which would be indicated by the wave *v*. This view we find has already been suggested by Francois-Franck and oth-

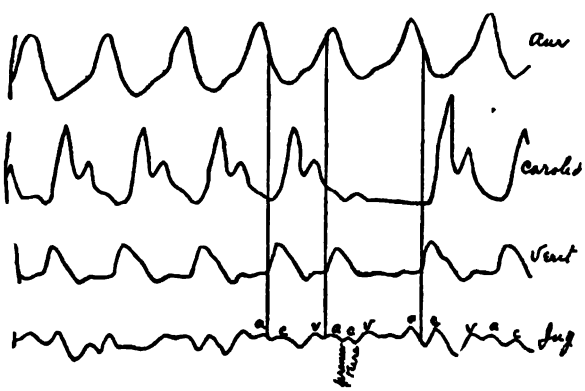

Figure 5.

ers. Our experiments are not sufficient to prove or disprove this explanation, but in verifying the dependence of the *v* wave on the occurrence of the ventricular contraction they lend a certain support to it. After *v* is completed a few very weak oscillations sometimes are observed in the tracing, but they may be neglected, as they are not constant and appear to be mainly due to the mechanism employed.

In some of our experiments the normal heart rhythm was disturbed by occasional electric shocks applied to the ventricle causing a contraction independent of the auricular impulse (ventricular extra-systole). One of these is shown in Figure 5, in which, while the auricle

maintains its usual rhythm, a weak premature contraction is seen in the ventricles and a minute movement in the carotid. A pause then follows in the ventricle and carotid until the ventricle is again aroused by the following auricular impulse. In the venous tracing the first alterations observed are a shortening of the *a-c* and the *c-v* intervals. The premature contraction of the ventricle explains the former, the shortness of the ventricular movement the latter, for in the only partially recovered ventricle the contraction is not only weaker than

Figure 6.

normal, but the relaxation is complete much sooner. After the *v* there succeeds a long pause until the following auricular systole causes a wave more marked than usual separated from *c* by a deeper depression. The pulse then resumes its usual form.

The increased size of the next *a* wave is probably due to the accumulation of the blood in the auricle through the latter chamber not having succeeded in emptying itself completely before the premature systole of the ventricle occurs. The large *c* is due to the powerful post-compensatory ventricular contraction. In some other experiments the *a* wave of the abnormal cycle was much increased in height and *c* very small. The increased *a*

is due to the inflow from the auricle into the ventricle being checked by the contraction of the latter, the pressure in the vein being suddenly increased accordingly. When the ventricle was stimulated soon after the last normal systole the contraction was sometimes so weak that no wave appeared in the carotid and the extrasystole caused no *c* or *v* in the jugular (Fig. 6).

When the auricle was stimulated electrically and an extra systole occurred, as in Figure 7, the most marked feature in the jugular pulse was an apparently exaggerated *v* wave. On careful measurement this was found to be compounded of the normal *v* of the preceding cycle and the *a* arising from the stimulus. The *c* followed this *a* apparently at the normal interval, and the

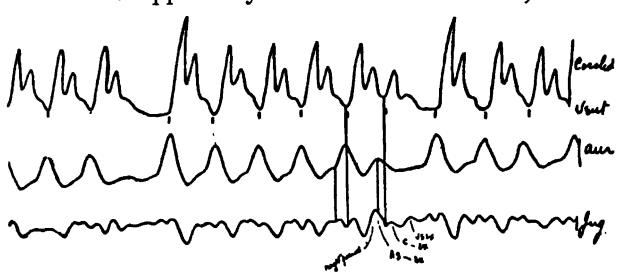

Figure 7.

chief further departure from the normal was the very slight development of the negative phase. Apparently the premature weak systole of the auricle was insufficient to empty it and the subsequent relaxation was too slight to relieve the accumulation in the vein.

CASE 1.—Mrs. D., aged 63, came under observation during September, 1906. A diagnosis was made of general arteriosclerosis, causing nutritional changes in the auriculoventricular fibers of the heart, thereby depressing their conductivity.

Except in December, when the tracings present nothing abnormal, the regular rhythm was varied by an occasional failure of the conduction, one fewer contraction occurring in the ventricle than in the auricle (Fig. 8). The auricular rhythm was perfectly regular, the ventricle simply occasionally failing to respond to one of

the auricular contractions. Here there was often further evidence of the failing conductivity in the fact that the last beat of the carotid occurred at an unusually long interval after the corresponding *a*. The blood failing to enter the full ventricle during the pause, the vein was more distended than usual and a large elevation occurred in the jugular tracing at the next *a*.

A more marked failure of the conductivity led to the omission of every third beat of the ventricle, two impulses from the auricle inducing contractions in the ventricle, the third having no effect. Here again the second beat of the carotid followed at a longer interval

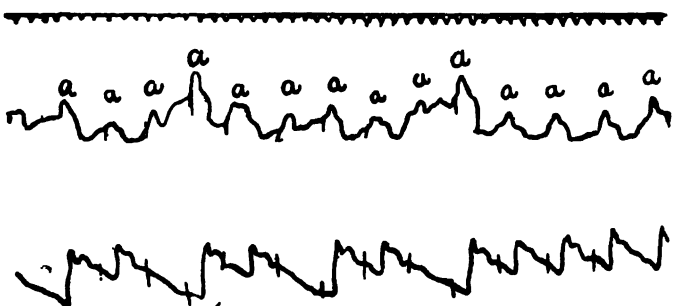

Figure 8.

after the *a* than the first, showing increasing fatigue of the conduction, which culminated in the complete failure of the third impulse to pass the block.

The next development of conduction failure is evidenced by every alternate impulse descending from the auricle failing to arouse the ventricle (Fig. 9). The contractions of both auricle and ventricle remain perfectly regular in the rhythm, but A = 2 V, i. e., half-rhythm is developed. After each ventricular beat there is an auricular contraction which is fairly normal in character except that no ventricular contraction follows. There is accordingly a slow escape of the blood from the vein, which becomes unusually tense and when the next auricular systole follows it finds the vein in this condition and the ventricle full. The second auricular con-

traction acting on a full vein thus causes a marked elevation and the subsequent auricular diastole along with the immediate inflow into the now empty ventricle allows the lever to fall to its lowest point. The tension of the full vein causes a more sudden rise and fall of the lever than in the first frustrated auricular contraction.

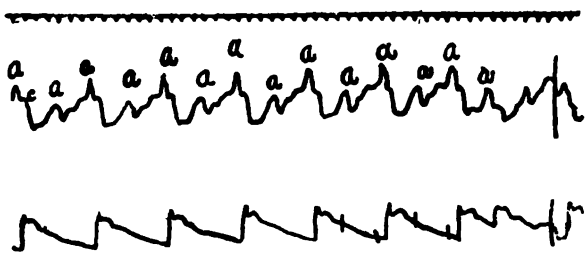

Figure 9.

Very frequently we have observed a curious anomaly occurring in the evidence of the accumulation of blood in the vein. For while this half-rhythm persists, the elevation of the jugular tracing may occur only every fourth beat of the auricle, although every second beat is identical in its relation to the ventricle (Fig. 10). This anomaly may occur at intervals in tracings in

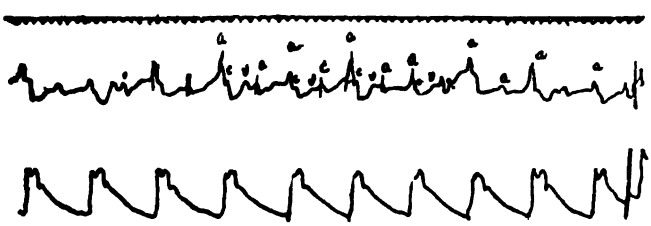

Figure 10.

which, as a rule, every second auricular contraction indicates backing up in the vein or may persist for a long period alone.

This elevation of the tracing is quite independent of the respiration, for it occurs when the breath is held, and the auricle appears to contract perfectly regularly whether the backing-up occurs in the vein or not. The

interval between the *a* and the radial pulse also seems to be the same whether the elevation occurs or not. In view of the conditions to be discussed, however, it seems to us probable that the presence or absence of this phenomenon must depend on slight variations between the auricular and the ventricular systoles, these variations either being too small to be recorded by the method or being concealed by some other factor in the tracing. In other tracings in which 2-1 rhythm was present the marked elevation occurred only every sixth beat and at one time only every tenth auricular contraction.

A still more marked degree of auriculoventricular arhythmia which persisted for many weeks is where the auricle beats five times to the ventricle's twice, or a 5-2

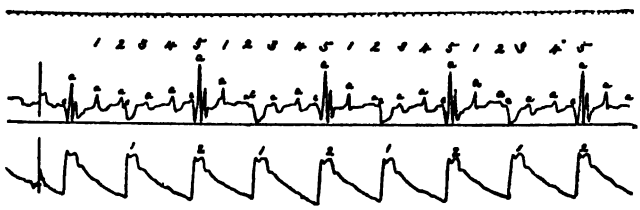

Figure 11.

rhythm. In this form the auricle and ventricle each preserves its perfectly regular rhythm, but in the auricular tracing there is a striking excursion at every fifth beat. The first *a* after this (Fig. 11) is also well marked without any subsequent depression, the second *a* is less marked with a deep depression, the third resembles the second, save that the depression is less deep, the fourth presents a stronger elevation with very slight depression, and the fifth has a marked rapid upward movement and equally rapid fall, and subsequent oscillation, after which the same cycle is repeated again an indefinite number of times. The radial pulse presents no variations whatever in rate or form.

This characteristic form of venous pulse is due to the fact that in the cycle of five no two contractions of the

auricle find the ventricle in the same phase of activity. The auricular contraction marked 2 (Fig. 11) is evidently the most efficient, for there is an immediate fall in the venous pressure indicating that the contents of the auricle have found easy egress into the ventricle; in fact, contraction 2 in the auricle has occurred at the same interval, before contraction 1 of the ventricle, as intervenes between auricular systole and ventricular systole in normal individuals. a^3 occurs at a less favorable phase in the ventricular movement, but the tension in the vein being reduced by the free outflow after a^2 there is comparatively little upward jerk and the diastole of the auricle permits of some inflow and corresponding fall in the vein pressure. a^4 finds a higher tension in the vein and also an unfavorable ventricular phase, and this

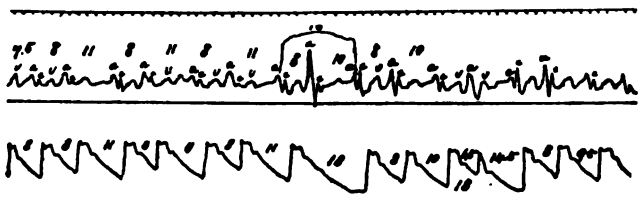

Figure 12.

is marked by a more sudden jerk upward and little fall afterward. The culminating point is reached in a^5, which apparently coincides with ventricular systole and in which probably no blood is driven onward by the auricular systole, but all is thrown into the vein which already shows signs of high tension; a^1 finds the ventricle in a somewhat more favorable phase and is correspondingly less marked, but only in a^2 is the optimum position for auricular systole again reached. The whole phenomenon is exactly similar to that described by one of us[3] as occurring in the dog's heart under various drugs which induce block and at the same time excite the ventricle to independent contraction. The changes in the position of a relative to the ventricular contraction

3. Jour. Physiol., xxv, 49.

can scarcely be made out in the ordinary tracings, but is put beyond question by the examination of those taken on fast running drums, which, however, occupy too much space to permit of publication.

In other tracings from this case the jugular pulse shows a cycle of seven *a* waves, while the radial pulse indicates three ventricular contractions. Every seventh *a* is exactly similar, but no two movements of the lever are identical in the cycle of seven. The explanation is the same as in the case of the 5-2 rhythm. In one tracing the jugular at first showed a 7-3 rhythm and then passed into the 5-2 rhythm which persisted throughout. There was obviously some change in the rate of the auricle or ventricle at the point where the 7-3 changed to the 5-2,

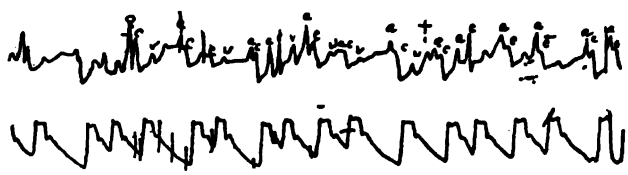

Figure 13.

and it was found that, while the ventricle retained its rhythm unchanged throughout, the auricle was rather slower when a 7-3 rhythm was present than when the 5-2 was developed, each of the 7 contractions occupying three and two-sevenths fifths, each of the five, three-fifths (3/5) of a second. Various other similar rhythms, such as 8-3, were met in this case, but no need for further discussion. The auricle never attained the rhythm of 3-1, though the fractions approached very close to this.

It is very difficult to determine whether there was complete block in this case or not. In the 5-2 rhythm every alternate beat of the ventricle was preceded by an auricular contraction which occupied the same relative position to it as in the normal beat. The other ventricular contraction was preceded by an auricular con-

traction at an interval about three times as great as the normal. If this beat arose from an auricular impulse, the time occupied in passing along the auriculoventricular fibers must have, therefore, been three times as long as usual. There seems, however, no explanation for this slow transmission, for there could have been no more fatigue of the fibers than in the other ventricular contraction, two inoperative impulses having passed along them in each case. Each alternate ventricular systole must, therefore, be regarded as arising in the ventricle without auricular impulse, and, granting this, it seems most likely that the whole ventricular rhythm was independent of the auricle in this phase.

This is rendered the more likely from the fact that when the auricular rhythm was slowed (in the 7-3 rhythm) the ventricle remained unchanged in rate. But if it be granted that there was complete block at these stages the further question arises at what point did this occur? There is a complete series of transitional forms from the 1-1 rhythm in which the conduction was adequate, through 3-2, 2-1, 5-2, to the 7-3 and 8-3 rhythms, and we find it quite impossible to state at what point the ventricle became independent of the auricular tutelage.

An important point is that in this complete block the auricle and ventricle each maintained a perfectly regular independent rhythm. The block did not seem to be affected by large doses of atropin, so that it was not of inhibitory origin.

CASE 2.—Mrs. P., aged 26. **Diagnosis, acute puerperal septicemia, with secondary toxic depression of the conductivity of the auriculoventricular fiber.**

The tracing in this case (Fig. 14) may be contrasted with that of the previous one in some respects, while there is a superficial resemblance between them in the fact that in each the radial pulse is slow while the jugular is much more rapid. The radial is more irregular than that of the first case, there often being alternation of long and short beats. The essential difference in the

two cases, however, is that no spontaneous ventricular rhythm has been developed in this one. Each ventricular contraction follows an *a* wave in the jugular tracing. Block is present, for many auricular impulses have no corresponding ventricular contraction, but no impulses are generated in the ventricle itself.

In some parts of the tracing the ventricle responds only to every third impulse of the auricle; in others the pause varies in length, the radial pulse alternately failing to follow two impulses of the three, and one of two; in others the beat of the ventricle corresponded alternately to three and to five auricular contractions. In some of those further evidence of failure conductivity was offered by the *a-c* interval. Thus in the tracing given (Fig. 14) the first *a-c* pause is 0.4 seconds; there

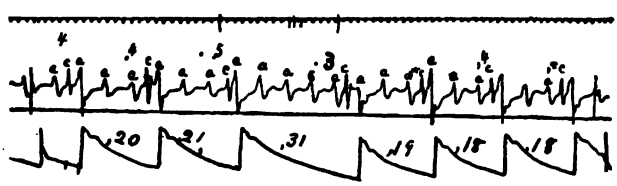

Figure 14.

then follow two inefficient auricular systoles, the third one being followed again at 0.4 of a second by a *c* wave. Then follow three inefficient *a* waves and the next *a-c* interval is 0.5 of a second. After a still longer pause in the ventricle (4-*a* waves) the *a-c* interval falls to 0.3 of a second and afterward 0.4 becomes the rule. The shortening of the *a-c* interval after the long pause at once suggests the recovery of the fibers from fatigue, especially as the preceding transmission was unduly prolonged as if from progressive exhaustion.

The difficulty arises, however, that during the long pause the fibers were being bombarded by a succession of impulses which, if transmitted, would have exhausted the conductivity just as much as if a ventricular contraction had occurred. It may be suggested, however, that the transmission was feeble throughout the auriculo-

ventricular fibers and that each consecutive impulse penetrated less deeply into them. While the upper end of the fibers was thus kept from regeneration by the constant receipt of impulses, its fatigue may have acted as a shield to an increasing length of the fibers measured from the lower end. Finally the regeneration of this part may have become so complete that it compensated for the fatigue of the upper end and an impulse passed at an unusual speed through the whole length of the fibers and originated a new ventricular contraction.

CASE 3.—Mr. K., aged 60. Diagnosis, carcinoma of stomach, with secondary anemia, cardiac irregularity due to changes in the rhythmic area of the heart (sinus venosus).

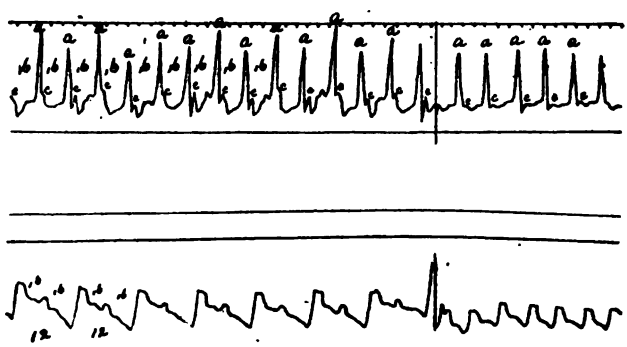

Figure 15.

Tracings from the radial and jugular sometimes showed a pulse fairly regular in appearance, though the variation between consecutive pulse lengths was greater than can be regarded as normal. But groups of two separated by rather longer intervals often occurred, as in Figure 12, where the pulse lengths are 8, 8, 11, 8, 11, 8, 11. The intervals between the waves of the jugular are equal to those of the radial, showing that these irregularities were not due to failure of conduction in the auriculo-ventricular fibers nor to the irritability of the ventricle.

The error in fact lies higher than the auricle, probably either in the rhythmic area or in the junction between this and the auricle. Occasionally, however, as in Fig-

ure 12, a pause of much longer duration occurs in the radial, i. e., 18 tenths of a second, during which the jugular tracing shows an auricular contraction at the usual interval, but this *a* is very much exaggerated and the subsequent oscillation suggests a high tension in the vein. The pause in the radial is practically equal to two previous intervals together and obviously the pause is due to the failure of the auricular impulse to cause a contraction in the ventricle. This may be due to failure of the auriculoventricular fibers, but the large oscillation in *a* suggests that the ventricle is in contraction, i. e., that there is here a ventricular extra systole. This view is strengthened by the fact that a few beats later a radial pulse occurs after 6.5 followed by a pause of 11.5 while in the jugular a wave occurs after 8 and 10 tenths. This is obviously a ventricular extra systole acting on a heart in which the rhythm is already irregular from changes in the rhythmic area.

Figure 13 has been added in order to give the general character of the jugular pulse in this case and in particular to show how much the *a* varies in appearance with the fulness of the vein, the vein becoming distended in the long pause, the succeeding *a* is generally more sudden and the fall more sharp than when the pressure is low. At the point marked "x" there is seen a distinct oscillation some time after the *v* and immediately before *a*. In some instances the oscillations actually overtop *a*. We have been unable to determine the conditions of its appearance or its significance, but it tends to appear during long pauses, although it is by no means present in all of these.

CASE 4.—*History.*—Mrs. W., aged 40, had been under observation for six years, suffering with mitral stenosis and regurgitation subsequent to rheumatism. March 23, 1907, she complained of dyspnea, cough and edema of the ankles, obviously from failure of compensation. The radial pulse was generally regular with the exception of an occasional ventricular extra systole. On examination of it on one occasion after

excitement and exertion, however, a typical pulsus alternans presented itself, shown in figure 15. The intervals between the successive beats were perfectly regular and even (each 0.6 of a second).

In the jugular tracing the *a* beats alternated in size in a very striking way and it is immediately seen that the larger *a* waves are those preceding the small ventricular contractions, while the smaller excursions of the jugular lever correspond to the large beats in the radial.

The rhythm of the auricle is quite regular and corresponds to that of the ventricle. On examining the tracing, the condition proved to be a simple pulsus alternans as described by Wenckebach.

It probably arose from an extra systole of the ventricle occurring some time before the tracing was taken. This extra systole was followed by a large slow ventricular contraction which was not completed when the next auricle impulse reached the ventricle and the consequent ventricular systole was weak and quick. The next impulse reaching the ventricle in diastole caused another slow and large ventricle movement which was not completed when the fourth auricular impulse arrived, and in this condition continuing caused the pulsus alternans registered in the radial tracing. So far the interpretation is that given by Wenckebach. The new feature is the alternation in the auricle, which appears to us to be purely physical; the *a* waves occurring before the ventricle is completely relaxed, a certain degree of obstruction to the outflow of blood from the auricle is met and this results in a larger wave than usual in the jugular. The next auricular systole occurs when the ventricle is relaxed, the inflow is freer, and the wave in the jugular is correspondingly smaller. We have added this tracing as an admirable demonstration of the importance of a point hitherto largely ignored, that the auricle must contract at a very definite point in the ventricular cycle if the optimum efficiency of the heart is to be attained.

Taken along with the tracing given in our first case, it shows that comparatively slight displacement in the auriculoventricular rhythm is sufficient to cause marked anomalies in the jugular pulse.

We think that more attention might be directed to the form of the auricular wave in the jugular pulse, and that as much information as to the state of the heart may perhaps be derived from this source as has occurred from the study of its time relations.

DISCUSSION.

DR. GEORGE DOCK, Ann Arbor, Mich., said that he knows of no problem in internal medicine more important than the study of the venous pulse. The important advances made in the knowledge of cardiac disease during the past five years give rise to the belief that greater discoveries may be made by the prosecution of the work along the lines of this paper. For fifty years heart disease was considered chiefly from a mechanical point of view. Before that Stokes and Graves appreciated the importance and value of the heart muscle; after that the pathologic anatomy was studied and physical diagnosis was cultivated, and the heart muscle was considered as a simple contracting muscle, working on mechanical valves. By the use of the knowledge given, physicians were enabled to make brilliant diagnoses, confirmed quickly by autopsy in many cases. From time to time cases of irregular character occurred and the diagnosis of the disease of the heart became more troublesome. Then physiology came to our aid. From the work of Gaskell, Engelmann, Wenckebach, Cushny and other physiologists, and the anatomic investigations of His and others, especially Aschoff, we recognize the heart at the present time not merely as a spiral mass of fibers, but as a very complex muscle having a peculiar set of functions, actuated not by the simple accelerator and inhibitory nerves, but by the fibers that are most conspicuous in the bundle of His. The results of such physiologic and pathologic anatomic studies enable us to learn more of functional alterations which give rise to important physical consequences. All this subject must be interpreted clinically by a study of the venous pulse. Most of the work must be done with instruments applied to the peripheral veins; some, perhaps, by sounds in the esophagus giving curves of the left auricle. But it is important to remember that at present we are not yet able to interpret all the waves seen. It is indispensable to have precise clinical investigations, such as Dr. Grosh has done so well, worked out

carefully by so careful and experienced a physiologist as Cushny and confirmed by the master mind of Mackenzie. When we consider the immense impetus given to the study of Adams-Stokes disease by the investigations of Erlanger, we can be encouraged in the hope that even more intricate clinical problems, and much more common ones, will in time be solved.

DR. ARTHUR HIRSCHFELDER, Baltimore, said that the essayists' interpretation of the C waves differs considerably from the interpretation Mackenzie placed on them in his recent communication, basing them on the very curves mentioned. The latter writer ascribes the C waves entirely to the carotid. It is interesting that Grosh and Cushny corroborate the observations of Morrow and Bard of Geneva and of himself in contradiction of Mackenzie. The V waves are very often difficult to interpret As shown by Mackenzie, and later by the experimental tracings of Hering, the V wave is coincident with the opening of the tricuspid valve. It is much easier to obtain a clear interpretation of the tracing by regarding only the fall and not the rise of the V wave. For the beginning of the descending limb shows at a glance when the tricuspid valve opens. In that case an interpretation of the tracing, before obscure, becomes clear. The reason that relatively unsatisfactory results are obtained in this work, except in Adams-Stokes disease, is that clinicians are in the habit of expecting too much from such tracings. One should remember, however, that except for tracings made with a stomach tube in the esophagus this method (Minkowski, *Deutsche med. Wochschr.*, 1906, No. 31), gives no idea at all of what goes on in the left side of the heart. It only pretends to tell of the changes occurring in the veins in the cardiac rhythm, and when the tricuspid valve opens. Therefore, the only points that one could expect to utilize by means of the venous tracings are: First, the presence or absence of tricuspid insufficiency. There are many cases where one finds cardiac breakdown, edema, etc., with the tricuspid valve closing. On the other hand, one frequently sees tricuspid insufficiency without symptoms of general cardiac breakdown. Secondly, by this means one may be able to determine the nature and origin of any irregularity, especially extrasystolic irregularities. You are also able to tell whether the irregularity arises in the auricle or ventricle. This is a point of particular importance, because any irregularities arising in the auricle are contraindications to the use of digitalis; while irregularities arising in the ventricles can frequently be cured by digitalis. In this sense the venous tracings may be of great importance. Again, one is able to determine the presence of partial heart block, or complete heart block. Partial heart block frequently can

not be determined by anything except a careful interpretation of the venous tracings. Here one may have to differentiate between the two kinds, partial and complete heart block, partial heart block due to vagus action, and that due to irritation of the fibers in the bundle of His. Here again one is confronted with a question of great practical importance in the use of digitalis. Digitalis heart block from the use of comparative small doses of digitalis, as shown experimentally, is due to the action of the digitalis on the vagus center. True organic heart block is due to a lesion of the fibers in the bundle of His.

Dr. George W. Norris, Philadelphia, urged the necessity of studying cardiac diseases by the method mentioned, and recommended for the purpose the Jacquet cardiosphygmograph. This instrument is small and portable. With it any three pulsations can be simultaneously recorded on smoked paper. One can thus obtain the impulse of the apex beat, the pulsation of the jugular vein, carotid artery and radial artery; or the respiratory curve, the impulse of the right ventricle, a pulsating liver or an hydrothorax. Its use in cases of Adams-Stokes disease in demonstrating the inco-ordination of auricles and ventricles is well known. The last named condition, however, may be present unexpectedly. In two cases in which he has had any opportunity of tracing, there was only slight dyspnea on exertion and a pulse rate of 60; the tracings showed a dropping out of ventricular beats due to depression of conductivity; the interesting question, of course, arose as to whether these were incipient cases of Adams-Stokes disease. He had further made tracings in a number of cases with anginoid symptoms referred to him by Dr. Musser. In such cases delayed conductivity, or prolongation of the period of tension, often sounded a note of warning that one had to deal with a degenerating myocardium. Often one is thus able to determine beforehand the cases which will be benefited or made worse by digitalis. In tricuspid insufficiency the type of the venous pulse confirms the diagnosis. In this connection it should be borne in mind that some authorities, among whom Gibson may be mentioned, maintain that primary tricuspid insufficiency is by no means so rare as is generally supposed. An interesting case which Dr. Norris had lately traced for Dr. Marvel showed multiple pulsations in the cervical veins and clinically seemed much like an early case of Adams-Stokes disease. The cardiosphygmograph, however, revealed the fact that the extra pulsations were ventricular in origin, due to feeble extrasystoles which failed to reach the wrist. Dr. Norris emphasized the fact that the study of the venous and arterial pulses coincidently is not merely of theoretical interest, but of great practical utility.

DR. L. C. GROSH, Toledo, Ohio, said that the endeavor of the paper is to aid in the analysis of the waves in the jugular pulse by an experimental method simulating the clinical ones used to-day. Lack of time made it impossible to present fully the clinical cases in which they attempted to demonstrate some of the applications of the jugular pulse, especially those pointing out some of the difficulties in demonstrating complete dissociation of auriculoventricular rhythm. In answer to Dr. Hirschfelder's criticism that Dr. Mackenzie misinterpreted their tracings Dr. Grosh stated that Dr. Mackenzie was confused by using the tracing taken before the jugular was dissected free from the carotid for the one after this was done.

THE SUDDEN APPEARANCE OF APNEA IN THE COURSE OF TABES DORSALIS AND ARTERIAL SCLEROSIS.

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The first patient, a young married woman 26 years old, had a syphilitic infection seven years ago. The past six months the patient has suffered from lancinating pains in the thighs and legs. She has also been annoyed with the feeling as though there was some substance interposed between the soles of her feet and her shoes. There have also occurred several attacks of nausea and vomiting, which, from her description, could very well have been gastric crises. Besides these attacks of nausea and vomiting there were no signs of vagus involvement.

Recently the thigh and leg pains grew so intense that morphin was required to allay the pain. The patient showed no disturbance of coordination. The pupils reacted sluggishly to light. The patellar and ankle reflexes were absent. The tactile sense and perception of temperature and of tuning-fork vibrations were unimpaired. There was, however, well pronounced hypoalgesia in the feet, legs and thighs, and the plantar surfaces of both feet exhibited a marked delay in transmission of the pain sense. The absence of patellar reflexes, the presence of hypoalgesia and delay in transmission of the sense of pain without trophic symptoms or any other signs, of multiple neuritis or syringomyelia, justified the diagnosis of tabes dorsalis. Dur-

ing the morning of the same day on which I examined her the patient was given ¼ grain of morphin hypodermically. About forty minutes after the injection of morphin the patient suddenly, and without the slightest sign of distress, ceased breathing and lapsed into a semicomatose state. The attending nurse used artificial respiration for about twenty minutes, when suddenly automatic respiration and consciousness were simultaneously resumed.

The patient had been given ¼ grain morphin hypodermically as I entered the house, and a few minutes after I had finished my examination there recurred the same symptoms seen in the morning. The patient became unconscious and ceased breathing. There was a slight cyanotic tinge to the skin of the whole body, the lips were pale and cyanotic. The pulse, which had been 80 up to the advent of apnea, now had a rate of 120. The radial artery widened its lumen. The diameter of the radial artery seemed to have increased threefold, but the maximum pressure was greatly diminished. At the same moment a pulsation in the dorsal veins of the hands was plainly visible. The pulsation was centripetal and strictly synchronous with the arterial pulse. The veins of the hands were dilated, but there were no signs of stasis from the right heart, either in enlargement of the heart's area of dulness to the right or dilatation of the jugular veins. In other words, the patient had vasomotor relaxation in the veins as well as in the arteries. The instant automatic respiration was resumed (after a lapse of about twenty minutes) all signs of vasomotor relaxation disappeared; the artery retracted to its original caliber. The veins retracted at the same instant to their usual size, the venous pulse disappeared and the pulse rate dropped from 120 to 80.

All these changes in the vascular phenomena occurred instantly and with the return of consciousness and automatic respiration. We did not permit the patient to remain in the apneic state for a longer time than thirty

seconds without employing artificial respiration. During the entire period of twenty minutes the apnea was unbroken by a single complete respiratory effort on the part of the patient. At the conclusion of a series of artificial respirations there would be a very slight indication of an inspiratory effort, but not sufficient at any one time to inflate the lungs. So during a lapse of twenty minutes the patient's sole respiration was artificial. There was a striking disproportion between the degree of cyanosis and respiratory disturbance. The slight cyanotic tinge to the skin seemed to be dependent on the vasomotor phenomena rather than on the apnea.

Another patient, a man 33 years old, who had a syphilitic infection eight years before, came recently under my observation. This patient had no ataxia, but he had unequal pupils which reacted sluggishly to light but more promptly to accommodation. The patellar and ankle reflexes were both absent, though he assured me the patellar reflexes were present only two weeks prior to the time he consulted me. This patient had a fracture of the internal malleolus of the left leg, crepitus could be elicited and, though the patient perceived the grating, it caused him no pain. The tuning-fork vibrations were clearly perceived over the whole body as well as over the fractured fragment. Perception of temperature was everywhere intact. The tactile sense also was normal. There was, however, a marked hypoalgesia over both thighs and legs and a marked delay in the transmission of pain over the hypoalgesic areas.

There was a clear history of gastric crises and intestinal crises accompanied by rectal hemorrhages; severe lancinating pains in the thighs and legs had persisted for three years, and there was hypotonia of the muscles of the thighs and legs. These symptoms were sufficient to convince me of the existence of tabes dorsalis.

The patient told me that a year ago he received a hypodermic injection of morphin (¼ gr.) for the relief of supposed sciatica. About thirty to forty minutes

afterward he suddenly lapsed into unconsciousness and ceased breathing and for fifteen or twenty minutes artificial respiration was employed. When consciousness and automatic respiration returned he could remember nothing of what transpired, so his loss of consciousness was complete. A few weeks later morphin was again given him for the same purpose, but this time only 1/8 grain of the drug with 1/100 grain of atropin were used. Exactly the same events followed as after the former dose of 1/4 grain. Apnea and loss of consciousness supervened about thirty minutes after the injection of morphin was given and lasted about fifteen minutes.

Both these patients on frequent occasions had received hypodermic injections of morphin on account of lancinating pains without the least untoward results. On account of the alarming signs which developed twice in each patient morphin was not again used for several months, but later injections of morphin were used without the development of any respiratory or circulatory symptoms.

Both these patients exhibited signs of profound hypoesthesia of the respiratory center at a time varying from thirty to forty-five minutes after the administration of morphin. This is the time which uniformly elapses between the administration of morphin and the maximum respiratory depression in animal experiments. Both the patients were in the preataxic state of tabes dorsalis. They were both in a period which marked the transition from symptoms of excitation to symptoms of depression. Both patients had suffered from involvement of the vagi as evidenced by gastric crises. Neither patient had any recurrent laryngeal symptoms.

There seems to have existed in these patients a certain depression of cellular response of the respiratory center, though insufficient to cause any symptoms. The added depressor effect of a small dose of morphin sufficed to cause hypoesthesia of the respiratory center and pre-

cipitated the attack of apnea. Though I witnessed only one of the four attacks mentioned, it seems reasonable to suppose the vasomotor symptoms described in one attack must have occurred in all, because in all the attacks there was loss of consciousness, and that depends on vasomotor and not on respiratory depression.

It seems certain death would have followed in each instance had not artificial respiration been employed by persons in attendance on these patients. We occasionally hear of death after the administration of small doses of morphin, and this experience suggested possibly there may be found in medical literature some fatalities which occurred in tabetic patients after administration of moderate doses of morphin.

Suppose one of these patients, suffering from what is believed to be sciatica (but in reality has the sciatic pains of an early tabes dorsalis) finds himself in a strange hotel and a physician is summoned who gives him a hypodermic injection of a quarter grain of morphin. In about fifteen minutes the acute pain is subdued and the patient is left alone. Should unconsciousness and apnea follow after the usual elapse of time I believe death would follow.

I was unable to find any such case reported in the Surgeon General's Library. All the reported cases of apnea or Cheyne-Stokes respiration following the use of morphin proved to be cases of cardiovascular disease, or patients who could not be said to have locomotor ataxia. With a single exception, in the literature on locomotor ataxia, the only respiratory symptoms described are the laryngeal crises. This exception is found in a case reported from Salpetrière in 1899 by Eggers.

This patient had tabes ten years. She was bedridden on account of paresis, muscular atrophy and ataxia. She had suffered many laryngeal, gastric and intestinal crises, so there was sufficient evidence of vagus involvement. This patient had a usual automatic respiratory rate of three to five to the minute. After eating a meal

or drinking hot liquids the respiratory rate would rise to thirteen to the minute and then gradually lapse to three or five to the minute. If the patient would take about ten deep inspirations, there followed immediately a total suspension of automatic respiration for sixty seconds, then automatic respiration resumed at the rate of two a minute, and within a few minutes rose to the usual rate of three or five. In this patient there was no disturbance of consciousness during the periods of apnea, and no vasomotor symptoms are described.

To avoid stimulation of the vagi by sectioning, Gad and Marckwald devised the plan of freezing both vagi, in a dog, and in this manner procured a bradyapnea of three or four a minute.

We find under other conditions a behavior of the respiratory center very like the cases above described. The one example of apnea with which all physicians are familiar is apnea at birth. Here we have a hypoesthesia of the respiratory center caused by the manner in which either the placental or umbilical cord circulation is affected during parturition. A sudden interruption of the placental circulation or a sudden compression of the umbilical cord stimulates the respiratory center of the fetus, and as a result the child is born asphyxiated from inhalation of the contents of the utero-vaginal tract. If the cord or placental circulation be very gradually obliterated for a protracted period, then exhaustion of the respiratory center follows and the child is born with apnea. Though generally automatic respiration is uninterrupted after once established, there are some cases on record in which lapses of automatic respiration occurred.

Morrow, of Montreal, reports the case of a child born apneic who, after the usual methods were employed for twenty minutes to stimulate respiration, breathed well. Several hours later apnea supervened and the child was cyanotic for half an hour; whether any automatic respirations occurred or not during this period is doubtful.

Artificial respiration promptly restored automatic breathing. During the following twenty-four hours there were twelve attacks of apnea, but artificial respiration promptly restored the child. The child later proved to be perfectly healthy.

In Morrow's case we have an instance in which cellular response of the respiratory center had been modified during parturition. Unusually prolonged treatment was required at birth to establish automatic respiration. After respiration had been established for a period of several hours apnea suddenly developed without the least premonitory symptom and reappeared twelve times within the first twenty-four hours of extrauterine life. Thus we have another example of modification of the respiratory center without symptoms other than the sudden appearance of complete apnea. In this case there was neither organic disease nor drug intoxication. During parturition the respiratory center was depressed to a point which required treatment for twenty minutes before respiration could be established, but the tone of the respiratory center was insufficient to prevent recurrences of apnea.

Another case of tabes dorsalis recently came under my observation in whom sudden death occurred during an attack of apnea. The patient was a man, 37 years old, who gave a doubtful history of syphilitic infection in 1887. Four years later his wife had two miscarriages. Since 1903 the patient had suffered from lancinating pains in the thighs and legs and irritability of the bladder with occasional enuresis. The pupils were unequal and reacted sluggishly to light and to accommodation. The patellar and ankle reflexes were absent. All sensory perceptions with the exception of the perception of pain were normal. Hypoalgesia was confined to the feet, legs and thighs. On the plantar surfaces of both feet there was a marked delay in the transmission of pain. There was not the slightest impairment of coordination either in the upper or lower extremities.

There was, however, hypotonia of the muscles of the thighs and legs.

A few weeks after I saw this patient he was seized with violent nausea and vomiting and epigastric pain. The patient was taken home and put to bed, suffering from a sense of profound exhaustion. He arrived at his home about 10 o'clock at night, and his family physician was summoned. The physician told me, during the time from 11 p. m. until 2 a. m., the patient had four attacks of apnea. Each period lasted a few minutes. About 2 a. m. the patient called to the doctor, who was in a neighboring room. By the time the doctor arrived at his bedside, respiration and heart beat had both ceased. No autopsy was made.

All these phenomena which I have described occurred in tabetic patients who were in the preataxic period and who could easily have been overlooked as cases of locomotor ataxia. In fact, one patient had been treated by diet and lavage for disease of the stomach, and one other was treated for disease of the prostate. In reality both patients were suffering from excitation symptoms of tabes.

In cardiovascular disease we see occasional lapses of respiratory activity which assume either Biot's or Cheyne-Stokes type of respiration. A man, 60 years old, with chronic aortitis, general arterial sclerosis, chronic interstitial nephritis and moderate hypertrophy and dilatation of the left ventricle, had for three months been suffering from nocturnal apnea, followed by prolonged apnea. For a year the patient had wakened frequently at night suffering from intense air-hunger; after breathing deeply for several minutes he would be able to go to sleep and rest for the remainder of the night. These attacks all came during the first hours of sleep. For three months he had been greatly distressed by complete suspension of respiration directly he fell asleep, and then awakened with intense air-hunger,

which was relieved after a few minutes rapid deep breathing.

It was discovered he could avoid this period of intense air-hunger if he were awakened directly apnea commenced. So his wife would watch him as he fell asleep and waken him the instant respiration ceased. This plan enabled the patient to escape the period of air-hunger which always followed spontaneous wakenings. Very commonly he would have to be wakened as often as a dozen times before respiration would continue after falling asleep.

This patient presented the type of Biot's respiration, a modification of Cheyne-Stokes respiration in which apnea and hyperapnea alternate without the gradual increase and diminution in rate and depth of respiration which intervene between the periods of apnea in Cheyne-Stokes phenomenon. Owing to sclerosis of the basilar arteries with consequent impairment of blood supply to the medulla he suffered what may be termed intermittent claudication of his respiratory center. There was not the slightest sign of impairment in the gross hydraulics of his blood circulation so far as the right heart, pulmonary circulation, liver or the pendant parts were concerned. There were no signs of respiratory involvement during his wakening hours, but the instant the added factor of sleep ensued there was induced a sufficient anemia of the respiratory center to cause apnea, and automatic respiration was resumed only after the partial pressure of carbonic acid in the blood reached a point sufficient to arouse his depressed respiratory center to action. This train of events explains those cases of arterial sclerosis which waken with suffocation during the early hours of the night when sleep is most profound, and when examined during their attacks reveal no signs of pulmonary stasis, no emphysema or bronchial râles and no change in character or rate of the arterial pulse. It is not a dyspnea; it is a prolonged hyperapnea, and has for its basis circulatory changes in

the medulla which are not insufficient to produce symptoms during the waking hours, but with the diminution of blood supply to the encephalon which comes with profound slumber a sufficient anemia of the medulla occurs to produce hypoesthesia of the respiratory center.

Here we have again (as in the tabetic patients) a sudden precipitation of apnea from a slight cause which is only a cumulative factor in betraying cellular changes in the respiratory center which are concealed until the sudden development of apnea.

All the cases of Cheyne-Stokes respiration which are produced in cardiovascular disease by the injection of small amounts of morphin occur in elderly people or patients with arterial disease. In all these patients we have the cumulative effect of morphin on a respiratory center already affected by an impaired blood supply. The patient above described recovered from his respiratory symptoms after taking nitroglycerin and caffein citrate, a further proof of the theory I have presented.

A man, 71 years old, had Biot's type of respiration, i. e., sharply alternating periods of apnea and hyperapnea. The periods of apnea lasted as long as sixty-seven seconds. There were clinical signs, of arterial sclerosis, high blood pressure, pulse of long duration, hypertrophy and dilatation of both the right and left ventricles of the heart, and renal infarcts. During the periods of prolonged apnea the patient talked irrationally and incoherently; during the periods of apnea there was profound slumber. This clinical picture had continued for nearly three weeks when nitroglycerin, 1/100 gr. every hour, and 5 gr. of caffein citrate every three hours were given. Though there was moderate edema of the legs, the improvement which followed the treatment could not be ascribed to increased renal elimination. Biot's respiration ceased and the mental symptoms all disappeared within a few hours. The patient died suddenly two days later with symptoms of embolus in the pulmonary artery.

I cite these cases because I believe in cardiovascular diseases we are too ready to assume all respiratory distress must be ascribed either to impairment in the pulmonary circulation or to diminished secretion of urine; when in reality we are dealing with an ischemia of the respiratory center, and the other factors are merely coincident to the respiratory phenomena and not their cause.

DISCUSSION.

DR. ALLEN A. JONES, Buffalo, said that he had seen only one case of this sort, but this one case was sufficiently striking to make its impress on him for all time. A man of middle age, with tabes, who had been a morphin habitué for a number of years, took his usual quantity of morphin and smoked excessively during his stay in the hospital. One night the nurse reported that the man had stopped breathing and was dying. He was cyanotic but, under the influence of nitroglycerin hypodermically, he began to breathe again. Dr. Jones went to the hospital and for two hours that man went from one spell of apnea into another, but he finally recovered. During the attack he was given strychnia and camphor hypodermically. A few days afterward the man said he would stop his morphin and resort to an old remedy that he had gotten from answering an advertisement. One morning he was seized again with a "dying attack," and stopped breathing for three minutes. During this time he became very cyanotic, his pulse was small and frequent, but he responded to stimulation. He had several such attacks during the day and finally recovered. He is in better condition to-day than he was last year.

DR. C. F. HOOVER, Cleveland, Ohio, said that he thinks such occurrences are not uncommon, although he searched the literature and was unable to find a single case mentioned. He believed that if he had another such case of tabes with apnea, instead of resorting to artificial respiration, he would probably invert the patient to stimulate the respiratory centers. The same result will follow this procedure here as in tachycardia. A patient had a pulse of 240 to the minute for twenty-eight hours. He inverted her, heels up and head down. That was not sufficient, but when she took deep breaths it brought the pulse down to 120. Her condition was due to postoperative depression. The patients should be held inverted for two minutes.

PHYSIOLOGIC AND CLINICAL OBSERVATIONS ON THE ALIMENTARY CANAL BY MEANS OF THE ROENTGEN RAYS.

G. E. PFAHLER, M.D.
PHILADELPHIA.

PART I. THE GASTROINTESTINAL TRACT.

The superiority of this method of examination over others is recognized, I think, by all who have investigated it sufficiently. To date, there have been about 55 contributions on the subject, and the method has reached a stage of development, when no case involving a chronic ailment of the alimentary canal is completely investigated until there has been a Roentgenologic examination by a competent man.

Cannon[1] by this method has added to our knowledge of the physiology of the gastrointestinal tract. Rieder[2] of Munich, however, was the first to place the clinical study on a firm footing. After the administration of large quantities of bismuth food he was enabled to obtain beautiful negatives showing the size, position and form of the stomach, and to a certain extent the rate at which the stomach would empty itself.

Holzknecht[3] advanced particularly the Roentgenoscopic method, and by means of the fluorescent screen he was enabled to study not only the points determined by Rieder, but also to recognize the peristaltic movements of the stomach walls, the effect of the respiration and the effect of massage on the contents of the stomach.

1. THE JOURNAL A. M. A., March 21, 1903: Anns. Surg., April, 1906; Am. Jour. of Physiol., vi, 123-149.
2. Munch. Med. Wochschr., Aug. 30. 1904.
3. Berlin. klin. Wochschr., Jan. 29, 1906; Mitteilungen aus dem. Lab. f. radiol. Diagnost. u. Therap., Vienna.

In America, the Roentgen method of examination of the gastrointestinal tract has been especially employed in the study of gastroenteroptosis by Hulst[4] and Pancoast.[5]

My studies began in March, 1905, after reading the excellent paper by Rieder. To date they include a study of 80 subjects. Thirty-one of these were healthy persons. The others include a variety of pathologic conditions, and were obtained in part from private practice, but in great part from the wards of the Medico-Chirurgical Hospital under the care of Profs. J. M. Anders, Judson Daland and W. Easterly Ashton, to whom I am especially indebted for the use of this material and for their kind interest in my work.

THE NORMAL STOMACH.

There has been much discussion as to the form and position of the normal stomach. Time and space will not permit of a review of the various types and the arguments in favor of them which have been described. The general idea of the form and the position of the normal stomach, as well as the text-book illustrations, has been obtained from a study of the stomach of the cadaver, the patient on the operating table, or clinically by means of percussion.

Practically all of these studies have been made with the body in the dorsal recumbent posture. The position of the stomach in the dorsal recumbent posture bears very little relation to its position in the standing posture. Percussion in the standing posture, I believe, is entirely unreliable, because in the standing posture there is present only a small collection of gas in the fundus of the stomach, and from this amount of gas it is impossible to judge of the size or position of the remainder of the stomach. If distended with food, its percussion note will be interfered with by the colon.

4. Phys. and Surg., September, 1905; Arch. Phys. Therap., January, 1906.
5. Univ. of Penna. Med. Bull., August, 1906.

Therefore, since we spend most of our active life in the standing posture, and especially during the hours of digestion, it is most important that we determine the form and the position of the stomach in this posture. I believe that the Roentgen method is the only accurate means of getting this information.

From the records in literature, it seems that most of the study has been on the sick, and therefore only very rarely is a normal stomach found. Holzknecht says he has rarely seen a normal stomach. For my own satisfaction, and to help solve this problem, I undertook a study of a series of healthy subjects. Most of them were physicians or medical students, together with a few healthy children. Most of the men were athletes and in the best of health. All were without symptoms at the time of examination.

I have examined in all thirty-one healthy persons. In this number I have found what I believe to be normal stomachs in fourteen. All the other stomachs presented the characteristics of gastrectasis and gastroptosis to a greater or less extent.

The normal stomach, I believe, when empty or when moderately filled, occupies the left side of the abdomen, and extends from the inner two-thirds of the left dome of the diaphragm to the median line, usually about an inch above the umbilicus. The upper two-thirds is almost vertical, and the lower third is nearly horizontal, making the general direction of the stomach slightly oblique. The essential point of the normal stomach is that the pylorus be on a level with the lower pole. This corresponds practically to the normal stomach described by Holzknecht and Leven and Barret. Leven and Barret[6] find the stomach of the suckling horizontal when the patient is in the vertical posture.

The ages of these healthy patients varied from 7 months to 38 years. Each person who had a normal stomach also had a normal body in every respect. I

6. Presse Méd., August, 1906.

could recognize no difference between the normal type in children and that in adults, and I believe there is no difference in general between the normal stomach of the child and that of the adult.

The stomach of the average individual in the standing posture extends to or below the umbilicus. It is vertical for more than its upper two-thirds, and the lower pole is distinctly lower than the pylorus. It also occu-

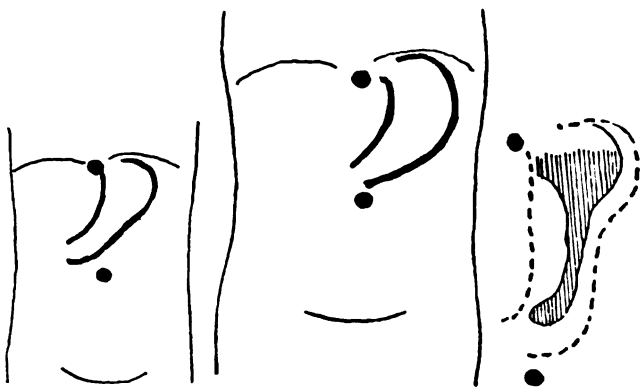

Figure 1. Figure 2. Figure 3.

Fig. 1.—A nursing infant, 7 months of age, after it has satisfied itself, and after taking about twenty grains of bismuth in a little water. Shows no particular difference from the normal adult stomach.

(Figures 1 to 9 represent Roentgenoscopic tracings which were reduced to lantern slides and then retraced, so that they show the actual form and proportions in each instance. The upper circular mark represents a cent placed on the ensiform cartilage and the lower circle represents a mark placed on the umbilicus. The first two figures show a lower curve representing the pubes. The curves in the upper portion of the figures represent the curves of the diaphragm. All of these figures represent the stomach in the upright position.)

Fig. 2.—A healthy female child of 3 years, showing the position of the stomach after taking six ounces of bismuth-kefir.

Fig. 3.—A healthy child of 10 years. The heavy central shadow shows the manner in which the normal stomach begins to fill. The clear upper space represents gas in the fundus, which increases as the food is swallowed. Gradually the stomach assumes the form represented by the broken lines.

pies the left side of the abdomen, except when distended; the pyloric portion extends from one to two inches beyond the median line to the right.

Two questions at once arise: 1. Why not consider the average stomach of healthy people normal? 2. Why

does this second type not produce symptoms if it is not normal?

The answers are that the second type has all of the essential characteristics of gastroptosis and gastrectasis. If this type is to be considered normal, then no line can be drawn between the normal and the gastroptosis and gastrectasis. Further, when these persons who show a slight gastroptosis and gastrectasis are closely studied they are found to have a tendency toward the narrow or flat chest in its lower portion. In other words, they are not perfectly proportioned.

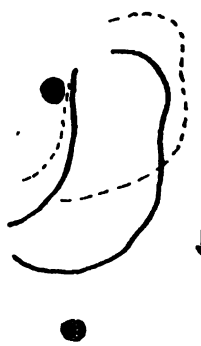

Figure 4.

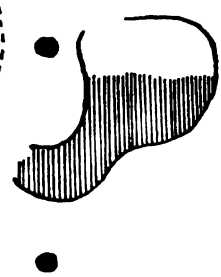

Figure 5.

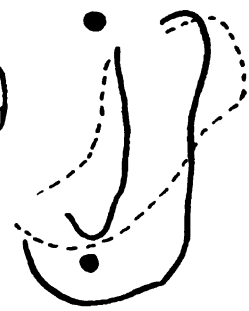

Figure 6.

Fig. 4.—A healthy man of 25 years, an athlete. The solid lines show the position of the normal stomach. The broken lines show the position of the stomach when the abdominal muscles were contracted, a rise of approximately three inches.

Fig. 5.—Shows a normal stomach in a man of 83 years, with the fundus widely distended with gas, which he swallowed.

Fig. 6.—Shows a mild gastroptosis in a healthy man of 30 years of age. The solid lines indicate the position of the stomach in his ordinary posture, while the broken lines show the stomach raised approximately to the normal position by contraction of the abdominal muscle and an erect posture.

The second question as to why no symptoms are produced can also be answered. In the persons I studied, when closely questioned, it was found that occasionally they suffered from indigestion, eructation of gas, with nausea, and some of them had even noticed dragging sensations at times or an uncomfortable sensation. These you see are simply the mild form of the graver symptoms associated with the severe grade of gastroptosis.

Further, these people were usually not as well nourished as the others. Therefore, I believe as long as the motility of the stomach is good no symptoms will be produced, but when this motility is impaired from any intercurrent cause symptoms will follow.

The arguments in favor of the normal type as recognized by both Holzknecht and myself are, first: It is the shape and position in which an engineer would build an organ to perform the functions of the stomach, these functions being to serve as a reservoir and partially to

Figure 7.

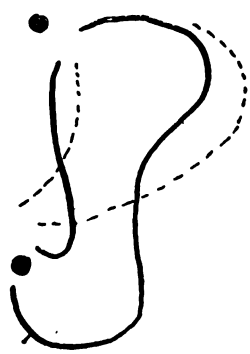

Figure 8.

Figure 9.

Fig. 7.—Shows a mild gastroptosis in a healthy man of 33 years. It shows that the manner of filling of the stomach, in which the muscular tone is good, does not differ from the normal. This figure shows the remarkable rise of the stomach to the extent of approximately six inches due to the contracting of the abdominal muscles.

Fig. 8.—Shows a more marked grade of gastroptosis in a healthy man of 24 years, and the marked increase in the width of the fundus as well as the rise of the lower pole on contraction of the abdominal muscles.

Fig. 9.—A thin healthy man of 34 years, with a phthisical chest, showing a well-marked grade of gastroptosis, and gastrectasis, and the remarkable rise of the lower pole to the extent of six inches due to contraction of the lower abdominal muscles.

digest the food. Nature has placed the secreting glands in the pyloric portion, and has also placed the strongest muscles in this portion, as is shown by the strongest contractions in this part. Therefore, the body of the stomach must serve as reservoir, and a reservoir is always placed higher than its outlet, and for this reason I believe the pylorus should be on a level with the lower

pole, as is found in the Roentgenographs of the normal stomachs and in the Roentgenoscopic tracings. Second, it is the type found in healthy children and in adults who have normally formed chests, strong abdominal muscles and who stand erect. Third, it is the position which the stomach assumes when the abdominal wall is contracted even in cases of gastroptosis.

The fact that the majority of people have gastroptosis is not new. In the discussion on enteroptosis in Berlin in 1890, Virchow[7] stated that in the majority of adults there is a certain amount of dislocation of the viscera, and especially of the bowel, so that more persons are affected with this dislocation than have the organs in normal position.

THE SUPPORT OF THE VISCERA.

The study of the healthy subjects, as well as the cases of gastroenteroptosis, show that the abdominal wall is the chief support of the abdominal viscera, and when this becomes weakened from whatever cause, such as relaxation after pregnancy, the removal of an abdominal tumor or cyst, ascites, rapid emaciation following obesity, or from general muscular weakness or faulty position, then gastroenteroptosis will develop.

In the 80 cases studied it was found that on contraction of the abdominal muscles the lower pole would rise from one to five or six inches; the degree of movement depending mostly on the degree of strength of the abdominal muscles and the degree of gastroptosis. As an example, the greatest movement occurred in a physician who was, generally speaking, healthy, but who had a well-marked gastroptosis, and yet in whom the abdominal muscles were still strong. In this man the stomach moved upward about six inches. In any healthy person if the abdominal muscles are willfully relaxed the viscera move downward, and when the normal tone is again obtained the stomach assumes a normal position.

7. Quoted by Holzknecht from Wiener med. Wochschr., 1903, 27, 28.

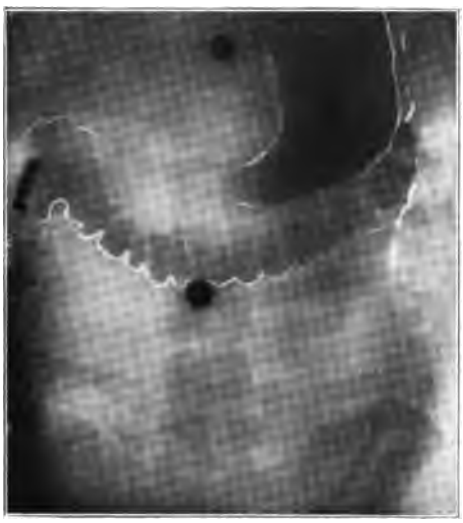

Fig. 10.—A Roentgenograph of a physician, 59 years of age, who in childhood had a phthisical chest, and by exercise and correction of posture developed a normal chest. Shows a normal position of the stomach and bowels. Dr. Daland's patient.

Fig. 11.—A Roentgenograph of a case of gastroptosis, taken with the patient lying with the abdomen on the plate, which accounts for the stomach showing approximately a normal position. Shows the collection of food between the kink in the duodenum and the pylorus, and separated from the food in the stomach by a sharp and regular line. A case of Dr. Daland's.

Sailer[5] believes that in the majority of instances splanchnoptosis is a congenital condition. I do not know on what that conclusion is based. I believe, however, that in all instances it is due to a weakness of abdominal muscles, or abdominal wall. No matter how early this condition is recognized, we need not assume that it is congenital, for sufficient cause for overdistension of the abdominal wall and therefore weakness can be found. All have recognized the tremendous distension of the abdomen of very young infants by gas. Why will not this overdistension produce the same weakness of the abdominal muscles that is produced by overdistension in adult life?

GASTROENTEROPTOSIS A CAUSE OF PHTHISICAL CHEST.

It has long been recognized that the phthisical chest and splanchnoptosis are associated. Just as all the abdominal viscera share in the descent, so the thorax shares in the effect. Why should it not? A body can not occupy two places at the same time. If the contents of the abdomen fall, therefore, something must take their place in the upper portion of the abdomen, or there will be a vacuum produced. Since Nature abhors a vacuum, an effort is at once made to replace the viscera, and as the result the diaphragm moves downward and the lower portion of the thoracic wall moves inward.

This is no idle theory, for it can be demonstrated in more than one way. If the stomach or bowels are rendered opaque, even in a healthy subject, and the abdominal wall relaxed, the stomach and bowel can be seen to move downward, and at the same time there is, to a lesser extent, a downward movement of the liver, spleen and diaphragm, while the thoracic walls clearly move inward. If, on the other hand, the abdominal wall is contracted, all of the viscera move upward and the chest expands. We need not depend, however, on Roentgenoscopy for this demonstration, for if the hands are placed on the thorax and the abdominal wall relaxed, the walls can be felt to move inward, and vice versa.

If the splanchnoptosis, therefore, is a cause of the phthisical chest, and since the weakness of the abdominal wall is an important cause of the splanchnoptisis, the rational treatment of these conditions will be the strengthening of the abdominal wall, if possible, by means of carefully regulated exercises, constant effort to stand erect, and the use of massage and electricity. I believe that many of the cases of gastroptosis of the milder type can be entirely relieved by this form of treatment. More than this, I believe that great assistance can be given, if given early, in transforming a phthisical chest into one of normal type, by strengthening the abdominal muscles.

An example of this came to my attention recently in a physician referred to me by Dr. Judson Daland. The examination was made because of an obstinate constipation, which was found by Dr. Daland to be due to hemorrhoidal obstruction in the rectum. This physician states that when a boy he had a phthisical chest, was therefore sent to the West to work on a ranch, and later joined the National Guard of Pennsylvania. The commanding officer constantly ordered him to contract his abdomen and to stand erect. To-day his chest is of normal type, and his stomach and bowels are in normal position, as the Roentgenograph demonstrates.

Many cases of gastroptosis, of course, can not be successfully treated in this way, because the abdominal muscles can not be sufficiently developed, and because there is present a marked gastrectasis. These must be helped by means of abdominal supports or operation.

In certain of the cases, in which the abdominal walls can be developed, it is rational to apply a bandage early in the treatment on the same principle, as stated by Dr. Daland in his lectures, that a surgeon applies a splint to a broken limb simply to support it until Nature can build its own support. The bandage will allow the patient to receive better nourishment, will relieve most

of the symptoms, and by increasing the general strength, will enable the abdominal muscles to gain their strength sooner.

THE PROPER APPLICATION OF A BANDAGE.

A bandage improperly applied will do more harm than good, as is shown by some of my illustrations. It is observed from the illustrations shown that even in marked cases of gastroptosis the stomach moves nearly into its normal position when the patient is in the supine position.

Therefore, a bandage applied to give support to the stomach should always be applied in the supine position, as was demonstrated by Dr. W. Easterly Ashton's patient. I believe the only absolute method of determining whether the bandage is doing its work properly is by means of the Roentgen examination. Therefore, the rays should be used first to determine the extent of gastroptosis, and the degree of motility, and finally to determine whether the treatment is accomplishing results.

RETENTION AND OBSTRUCTION IN GASTROPTOSIS.

The retention of food is, I believe, due in greatest part to the sac formed by the pendant portion of the stomach which sags below the pyloric orifice, but as long as the motility remains good the food is lifted out of this sack by means of the peristaltic contractions. I have never observed distinct gastric obstruction within the stomach, even in those cases which Pancoast classes as the kinking stomach, due to its extreme ptosis, because I believe in these cases the stomach is widely dilated and I have always found the food to pass easily from one portion to the other, when influenced by massage or muscular contraction. If this kink actually caused obstruction, the second portion would be found empty. In my experience they have been equally filled, and finally the food rests simply on the lower curvature at the lower pole, as some of the illustrations show.

There is a point of distinct obstruction, however, but

it is in the duodenum. It occurs about an inch from the pylorus, and in a number of the illustrations may be seen small portions of food resting between the pylorus and a point an inch away. This obstruction I believe to be due to a kink in the duodenum at this point. G. G. Davis,[5] in discussing the anatomic relations of the stomach, says:

> The pylorus is almost entirely surrounded by peritoneum, as is also the duodenum, for its first inch. Thus we see that the pylorus is extremely moveable within a short radius. The next eight or nine inches of the duodenum are, however, firmly fastened to the spine and the structure lying on it being covered by the peritoneum only in front.

Therefore, it is seen that the kink which I describe and which is illustrated by the Roentgenographs corresponds exactly to the point of firm attachment of the duodenum to the spinal column, which begins one inch from the pylorus.

The recognition of this obstruction will serve at least in some cases to differenetiate retention of food due to simple gastroptosis and that due to a neoplasm. The failure to recognize this point led me to err in a diagnosis recently. A patient of Dr. J. M. Anders, aged 48, had a series of chronic gastric symptoms, he had lost some weight, the HCl was practically absent, and at times when I moved my hand upward I thought I could feel it glide over a small mass in the region of the umbilicus. This mass was evidently gas crowded upward into this kink, for I could never feel it when I moved my hand downward. By Roentgen examination I found food retention of at least eleven hours. There was present constantly, food outside of the pylorus, as shown in the Roentgenograph, but I misinterpreted it, believing there was a carcinoma of the pylorus causing this obstruction, with which diagnosis Dr. Anders did not concur. I recommended an operation, which was performed by Dr. Ernest Laplace. He found no new growth, but found a marked gastroptosis which I had, of course,

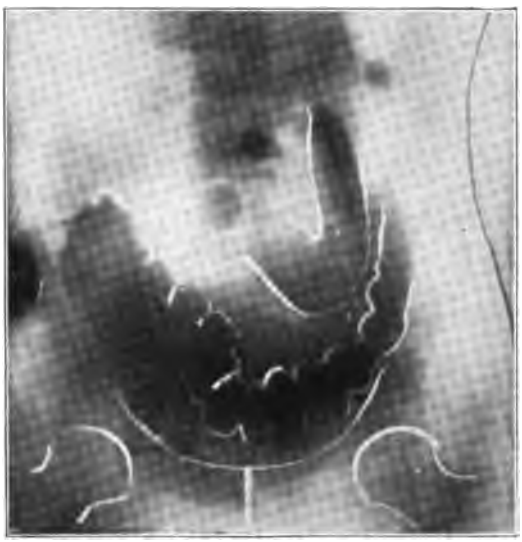

Fig. 12.—A Roentgenograph of a marked case of gastroptosis, and the retention of half of the food given six hours previously, showing not only no assistance from an improperly applied support, but probable actual interference with the motility of the stomach. Dr. Ashton's case.

Fig. 13.—Showing a support properly applied and the stomach in nearly a normal position in the above case.

recognized, and which is plainly shown in the Roentgenograph, the lower pole resting in the pelvis. A gastroenterostomy was done and the patient is doing well.

We can have a gastroptosis, together with malignant obstruction, as I have demonstrated, but when the obstruction is due to carcinoma of the stomach it is likely to occur to the left of the pylorus and not beyond it. At least, the obstruction will not present the typical appearance shown in the cases of simple gastroptosis. A sharp line of separation can often be seen between the food in the stomach and that lying outside. The sharpness of this line helped to eliminate carcinoma of the pylorus in a case of Dr. Daland.

I have studied cases of advanced carcinoma at the pylorus, but the length of this paper will not permit a review of them. Carcinomas that were not palpable have been recognized by Holzknecht, Grunmach and Steyrer.

HOUR-GLASS CONTRACTION DUE TO CARCINOMA.

History—The patient, a white man, aged 36, a musician, was referred to Dr. Warren C. Batroff. He was well until a year ago, when he consulted his physician on account of pain in the stomach immediately after meals. Dr. Batroff found a hyperchlorhydria and made a diagnosis of gastric ulcer. More recently he had felt a gnawing sensation, had lost his appetite and his strength, and had vomited blood. He could eat only small quantities of food at a time, which led Dr. Batroff to suspect an "hour-glass contraction."

Examination.—With the stomach empty, Roentgenoscopic examination showed a small quantity of gas in the fundus. When the bismuth capsule was given, it was found to lodge about two and one-half inches from the upper pole, and at the bottom of the collection of gas. (This much may at times be observed in healthy stomachs.) When the bismuth-kefir mixture was given it was found to lodge at this point for about a half hour, gradually trickling through. As the quantity was increased, in both the upper and the lower segments, it assumed a typical hour-glass appearance and the constricted portion did not dilate even when distended to the limit of endurance of the patient. A Roentgenograph made an hour after the food had been given permitted one to recognize not only the hour-glass contraction, but at the point of stricture

the walls of the stomach were seen to be very irregular, and something could be seen separating the wall of the stomach from the bowel, which had been rendered opaque by his previous treatment with bismuth subnitrate. Therefore I concluded that the hour-glass contraction was due to carcinoma.

The diagnosis of hour-glass stomach must not be hastily made, and never until the stomach has been distended to the limit.

THE INTESTINES.

The study of the passage of the food through the intestines is of importance. To study the small bowel the food must be introduced by mouth. To study the colon an enema containing bismuth may be given just preceding the stomach examination, or food may be given by mouth the preceding day, or two days may be utilized in the examination. This latter method is probably the best, because it gives rise to fewer complications and difficulties. Finally the bowel may be distended with gas. A single case will illustrate the value of following the food through the intestines.

History.—The patient, a boy, aged 18, was referred by Dr. J. M. Anders. His symptom was obstinate constipation. He had distinct gastroenteroptosis, but the most interesting fact observed was that, at the end of six hours after taking the bismuth-kefir food, it was all found lodged opposite the ileocecal valve, and gradually crowding its way through a very small orifice. In no other case had I recognized any such obstruction. Twelve hours later this portion was entirely empty, and the food could be observed evenly distributed through the colon even to the rectum. There was no delay due to decrease in the peristaltic movements of the large bowel. It lodged in the rectum, however, for another twelve hours. Therefore we concluded that his constipation was probably due to a spasmodic condition of the ileocecal valve and of the sphincter ani.

CONCLUSIONS.

1. The Roentgen examination will demonstrate obstructive disease anywhere along the alimentary canal, and much information as to the character of this obstruction can be obtained.

2. The Roentgen method of examination is probably most useful in the study of the stomach. By this means the size, form, position, its motility, its mobility and the effects of massage, respiratory movements, abdominal contractions, peristaltic action and the effects of food can be studied.

3. The normal stomach is slightly oblique in the standing posture, Approximately, its upper two-thirds is vertical, and the lower third is nearly horizontal. Essentially, the pylorus must be on a level with the lower pole. Its lower pole is usually an inch above the umbilicus, but moves downward when fully distended. The stomach is normally a very movable organ, as is shown by the fact that about two-thirds of it crosses the median line when the patient lies on the right side. When distended with food the pylorus is carried downward and to the right. I believe there is no difference between the normal stomach of children and the normal stomach of adults in the standing or upright posture.

4. The respiratory movements cause the upper pole to move to the extent of the movements of the diaphragm. The lower pole moves from one-half to one inch, between forced inspiration and forced expiration. With deep inspiration, the fundus is increased in diameter and the pylorus moves to the right.

5. The contraction of the abdominal muscles will cause the stomach to rise from one to five or six inches, depending on their strength and the degree of ptosis. However, in extreme gastroptosis the stomach may lie below the elevating force of the contractions.

6. These abdominal contractions may be used to mix the food in the stomach. If a person eats an ordinary meal and then takes an ounce of bismuth it can be thoroughly mixed with the food in a minute or two, and then studied with the rays.

7. These abdominal contractions seem to stimulate the peristaltic movements. Therefore, they assist in emptying the stomach by raising it so that it serves as

a reservoir, by removing the obstruction which is caused by the kink in the duodenum, and by stimulating the peristaltic movements.

8. These contractions cause not only the stomach to rise, but the entire abdominal viscera. The lower portion of the chest expands and diaphragm rises.

9. The reverse conditions develop when the abdominal wall is relaxed. In other words, the tendency in a normal person to splanchnoptosis may be seen when these walls are relaxed.

10. I believe, therefore, first, that the abdominal wall is the main support of the abdominal viscera; second, that the phthisical chest may be secondary to the descent of the viscera; and third, that the most important element in the treatment of the gastroptosis and the phthisical chest is the strengthening and toning of the abdominal walls and the correction of posture.

11. In severe grades of gastroptosis, the portion of the stomach that rests below the level of the pylorus serves as a retention sac, but the point of actual obstruction to the passage of food is a kink formed in the duodenum about one inch from the pylorus, where it is firmly attached to the spinal column. The food lying between this kink and the pylorus is usually separated from the food in the stomach by a sharp and regular line. This will serve as a differential point between this form of obstruction and that caused by carcinoma of the pylorus.

12. The Roentgen rays are of value in collecting additional information in the diagnosis of carcinoma of the stomach, but must not be depended on to make an absolute diagnosis.

13. When a supporting bandage is applied in the treatment of gastroptosis, there should, if possible, be a Roentgenologic examination to determine whether it is properly applied and whether it is serving its purpose.

14. A moderate gastroptosis may be present and not produce symptoms, as long as the motility of the stom-

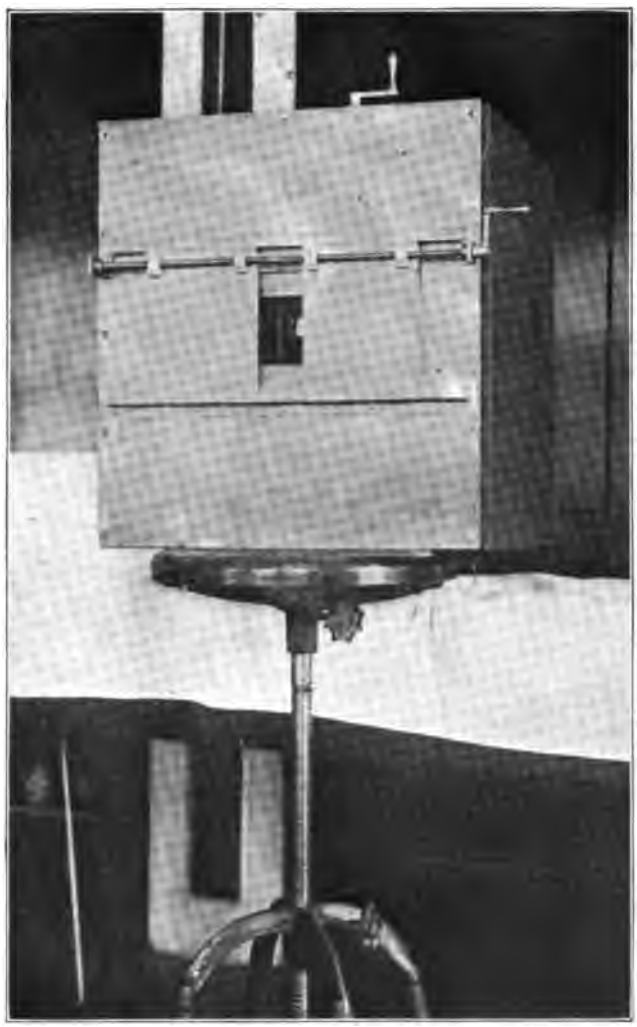

Fig. 14.—Lead covered case for holding the Roentgen tube.

ach is good. If, however, the motility of the stomach be disturbed by some intercurrent cause, then symptoms will be produced.

15. The Roentgenoscopic and the Roentgenographic method of examination each has its advantage. Roentgenoscopically, we study the motion of the viscera, while Roentgenographically, we make accurate records and often obtain finer detail.

16. The Roentgenoscopic method is a dangerous procedure to the operator, unless he is properly protected, and even then the amount of exposure should be reduced to the minimum.

17. The bismuth-kefir mixture (bismuth subnitrate 1 ounce, and kefir 1 pint or more) is the best medium to render the alimentary canal opaque, because it is easily digested, holds the bismuth in suspension almost perfectly, and because it tends to counterbalance the constipating effect of the bismuth.

18. The esophagus can best be studied by oblique illumination. Peristaltic movement can be seen carrying the food downward. Solids are likely to lodge for a short time at the level of the arch of the aorta, but pass quickly through the cardiac orifice. A swallow of liquid, on the other hand, lodges in the lower third of the esophagus for a period of about seven seconds before all of it passes into the stomach. It is probably detained at this point by the sphincteric action of the cardiac orifice, which only allows the liquid to pass in slowly. The capsule drops through, probably before the sphincter has had a chance to act.

PART II. TECHNIC. SPECIAL APPARATUS.

At first, because of the extreme danger to the operator connected with Roentgenoscopic examinations, I depended on plates entirely. Recently I have designed protecting devices which are both efficient and practical, and, therefore, have added to the Roentgenographic the greater knowledge which can be obtained from the Roentgenoscopic method.

The Roentgenoscopic method enables one to study the stomach in various directions and positions, its peristaltic movements, the course of the food through the empty stomach, to note its changes as it becomes filled, the effects of massage, the effect of the respiratory movements, and, what to me is of the greatest importance, to study the effects of the contraction of the abdominal muscles.

The advantages of the Roentgenographic method are that it makes a permanent record, and often gives greater detail and accuracy than can be obtained from the Roentgenoscopic method alone.

PREPARATION OF THE PATIENT.

The stomach, bowels and bladder should be empty if possible. A purgative should be given the day before, and if the bowels have not moved an enema should precede the examination. Depending on the information desired, an ounce of bismuth may be given after a regular full meal, and this mixed with the food by means of massage or muscular contractions.

If the patient is examined at mid-day a light breakfast may be given, unless carcinoma is suspected, when no food should be given, because the lodgment of food in the stomach may give appearances suggesting neoplasma. No patient should have food immediately preceding the examination.

Men need no special instructions regarding dress. Women should wear their shoes and stockings and a kimona or a special muslin gown. This special muslin gown hangs from the shoulders; it is slit in front to the level of the pubes, and posteriorly over the lumbar region for a distance of about ten inches. These slits are closed by strings. Through them the necessary landmarks are determined, and cents are attached to the ensiform cartilage and the umbilicus, respectively, by means of adhesive plaster.

APPARATUS.

A good tube and coil are the first requisites. Appliances will be necessary which will enable a Roentgenograph to be made in any position. Roentgenoscopic apparatus is necessary. For this I have designed special apparatus, with the chief object in mind of protection to the operator.

The first essential is a dark room. It should be absolutely dark so that the eye of the operator can be accommodated to the shadows on the fluorescent screen. It is difficult to make any well-lighted room temporarily dark. Therefore, I have recently adapted my "dark room" for this purpose. All the apparatus is in an adjoining room. The rays are passed through the door of the dark room before reaching the patient. Therefore, all light is excluded, and the patient is not frightened by any noise from the machine, nor is there danger of the patient touching any of the wires. In addition, this door cuts off the soft rays, and I doubt whether it would be possible to burn the skin of a patient under these circumstances. The operator should remain in the dark room fifteen minutes before beginning the examination.

A ROENTGENOSCOPIC TUBE-BOX.

In order to keep the room dark and exclude even the fluorescence of the tube, it must be encased. For the sake of protection to the operator and the patient, this case must be opaque to the rays. An adjustable opening in this case must be provided so that the field of rays is under perfect control. Finally, this case must be movable in all directions.

I have met these requirements by building the case (Fig. 14) of lead one-fourth inch in thickness; the front at least should be of this thickness of lead.

An opening in this front is made five inches square. This opening is controlled by four doors, each being one-half inch in thickness. These move equally from the

center in either the horizontal or the vertical direction. They are under perfect control in either direction and are worked by means of a two-way screw, which is turned by a crank. The box is cumbersome, but it is raised or lowered by means of a screw, and its base is on rollers so that it can be moved in any direction.

The fluorescent screen is covered with lead glass and is supported on a separate stand, which is adjustable. A second lead screen one-fourth inch thick is provided for the operator, behind which he stands and watches the Roentgenoscopic picture through a heavy lead-glass window.

In my hospital work I have this Roentgenoscopic tube-box hung from the ceiling and running on a track (Fig. 15). To it is attached the fluorescent screen, and both are moved upward and downward together, giving orthodiagraphic effects, by always keeping the center of the screen opposite the anode of the tube. All other orthodiagraphic apparatus is too dangerous to the operator, and the slight increase in the knowledge obtained does not justify this dangerous exposure.

I am not sure that even this extensive protection is perfectly safe, but I believe when properly used it is practically safe. I control the current by means of a pendant switch, which is carried in my hand, and by means of which I can control the time of exposure perfectly.

DANGERS OF FLUOROSCOPIC EXAMINATIONS.

When we consider the Roentgenologists who have lost their lives or damaged their bodies by doing fluoroscopic work, it is a debatable question whether any amount of additional knowledge gained over the Roentgenographic method will justify this danger, even though it is slight. The expert Roentgenologist, however, only needs a few seconds at a time to draw his conclusions, and by having a pendant switch in his hand he can control the current perfectly and thus reduce the danger to a minimum.

A patient examined by these flashes, and by means of

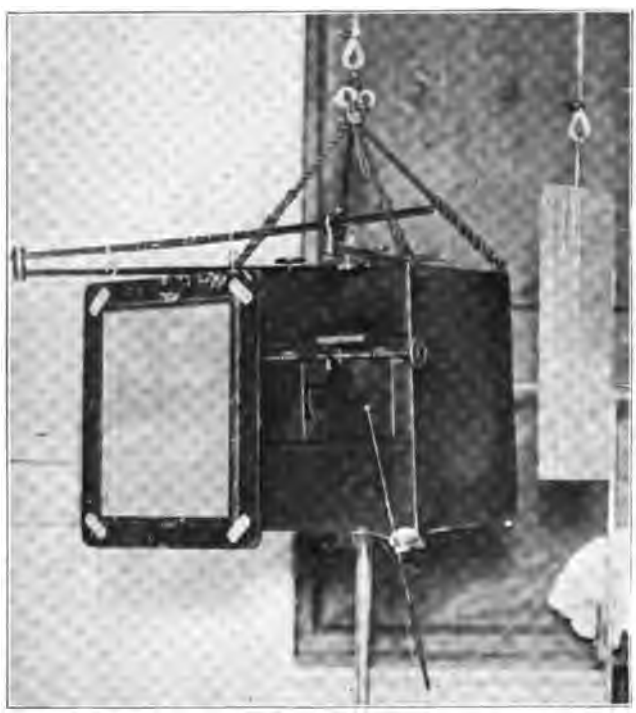

Fig. 15.—Showing method of hanging Roentgenoscopic tube case from track attached to ceiling.

the diaphragm above described is, in my opinion, entirely free from danger. First, because the actual time is too short to produce a burn, and because the small diaphragm makes it necessary to change the point of entrance of the rays continually. By this means no part of the patient's body gets more than a few seconds' exposure, or at most only a few minutes. So far, I have never had the slightest redness of the skin nor the least complaint from the patient from any of these examinations.

DIFFERENTIATING MATERIAL.

In order to render the gastrointestinal tract visible by means of the rays, some material must be introduced which is either more opaque or less opaque than the surrounding tissue. For this purpose we have practically narrowed our materials to two: one is bismuth subnitrate and the other is gas. Gas may be introduced either directly or may be generated in the tract by means of effervescing solutions.

The ideal bismuth food or mixture must be of a definite composition, easily and quickly prepared, easily digested, easily taken, not disagreeable in taste, and must in no way be harmful to the patient. It should suspend the bismuth for several hours.

A number of substances have been used with more or less success, such as milk, milk-broth, gruel, mashed potatoes and mucilage of acacia. Gruels require considerable time in preparation and in eating, and are liable to cause fermentation in the very cases in which these examinations are needed. The same objection applies to mashed potatoes and milk-broth. Therefore, the two that have been most commonly used have been milk and mucilage of acacia. The objection to these is that they do not suspend the bismuth well.

At the suggestion of Dr. W. Easterly Ashton, I investigated kefir. I compared the kefir with milk, mucilage of acacia, and mucilage of acacia and water, by placing a definite quantity of bismuth in each of four test tubes,

and filling them with four different media. After shaking and mixing them well, I immediately took a Roentgenograph and found that at least a fourth of the bismuth had dropped out of the mixture within a minute in both the milk and diluted mucilage of acacia. At the end of ten minutes nearly all of the bismuth had dropped to the bottom in the milk mixture and the diluted mucilage of acacia (Fig. 16). In one hour, the bismuth had sedimented completely in the milk and the diluted mucilage and had nearly all sedimented in the pure mucilage, while in the bismuth-kefir mixture, the bismuth was still well suspended, and remained so for at least sixteen hours (Fig. 17), and really remains well mixed at the end of a week. Of course, at the end of this time the milk serum has separated, but the bismuth apparently remains uniformly mixed with the casein, and when poured out of the test tube it does not come out as a clot, but in flocculent masses. Therefore, the milk is the least valuable to suspend the bismuth, and the kefir is by far the best. The advantage of this is that it enables us to obtain a shadow of the upper curve of the stomach as well as the lower. The difficulty of showing the lesser curve has been a criticism of our work.

The kefir is easily obtained in a large city, easily digested, quickly prepared, keeps several days on ice, is not disagreeable in taste, and can do the patient no harm. Its laxative qualities, I think, account for the fact that in almost none of my subjects studied were there constipating effects of the bismuth.

The question of toxicity of these large doses of bismuth naturally arises. Pancoast and Sailer[5] have observed toxic symptoms. So far as I have been able to learn from the review of the literature of this work, they are the only ones that have observed toxic symptoms. Rieder, Holzknecht and Hulst state distinctly that they have not observed any ill effects. I have never given any attention to the bismuth in the gastrointestinal tract, have

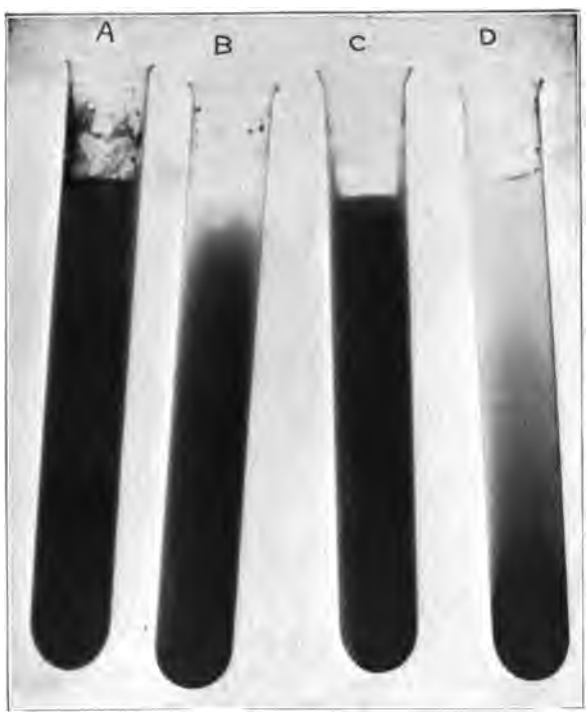

Fig. 16.—Roentgenograph of test tubes containing various differentiating materials. A, kefir and bismuth; B, water and equal parts of mucilage of acacia and bismuth; C, mucilage of acacia and bismuth; D, milk and mucilage of acacia.

often had two ounces in at one time, and have never observed the slightest ill effects. I always insist that the bismuth subnitrate must be pure and free from arsenic. Dr. Pancoast found his bismuth to be pure.

In order to study both the stomach and the colon at the same time, I often give an ounce of bismuth, which passes through to the colon, and in twenty-four hours after this I give an ounce which outlines the stomach and gives me their relative position, as is shown in a number of my Roentgenographs. I think, however, that we can reduce the amount of bismuth considerably.

The same results can be obtained by outlining the bowel and the stomach at the same time, by giving part of the food by mouth and giving an enema of bismuth and mucilage of acacia or oil just before making the examination. I have found that this mixture can be carried to the ileocecal valve in ten minutes, by having the patient first lie on the left side and then assume the knee-chest position. When it is desirable to outline a solid growth, the colon should be inflated with air. By this means the entire colon may be beautifully outlined and contrasted with the tumor.

Schwarz[8] devised what at first seemed to me an ingenious method, resembling somewhat the Sahli method of testing the digestive power of the gastric juice. He prepares a series of capsules of gold-beater's skin containing bismuth and pepsin, then places them in various solution of hydrochloric acid, and places them in the incubator to observe the time of digestion of the membrane, and, therefore, the time of release of the bismuth. He then applies the same to the stomach and observes the time of release of the bismuth by means of the Roentgen rays and by comparing with the incubator digestion judges the amount of HCl present in the stomach. He also mixes cork with other capsules and gives two, one of which will sink to the bottom of the stomach and the other will float on the liquid in the stomach,

8. Ztschr. f. Aerztl. Fortbild., 1906, No. 12.

and in this way he can estimate the time of passage of an ordinary meal from the stomach. I have repeated these tests in the incubator, and find that the capsule releases the bismuth in about one-fifth of the time if it is gently agitated, as it would likely be in the stomach, and, therefore, not only the amount of hydrochloric acid in the stomach will influence the rate of dissolution of the capsule, but also the degree of motility and the amount of rough handling that the capsule may receive from impact with other coarse food. I believe, therefore, that it is of no practical use.

THE STUDY OF THE ESOPHAGUS.

The esophagus is best observed by oblique illumination, either by placing the tube anteriorly and the screen posteriorly, as has been usually done, or by a method which I believe is better. The tube should be placed posteriorly to the left and the screen anteriorly to the right, passing the rays between the heart and the spinal column. On account of the divergence of the rays, the heart is thrown well anteriorly and the shadow of the spinal column well posteriorly, leaving a rather wide space in which the esophagus can be observed through its entire course. This, of course, exaggerates the size of the esophagus very much, but since we are usually only interested in the recognition of dilatations or contractions or diverticuli, which are likely to be local, we can estimate the degree of dilatation or the size of a growth. It is very interesting to watch the movements of food through the esophagus. If the patient is allowed to swallow a capsule of bismuth it usually lodges for a second or two at the level of the arch of the aorta. It then passes downward and quickly into the stomach. I have never found a capsule to lodge at the cardiac orifice except in cases of stenosis. On the other hand, I have only observed obstruction to liquids at the level of the aortic arch in a case of general thickening of the

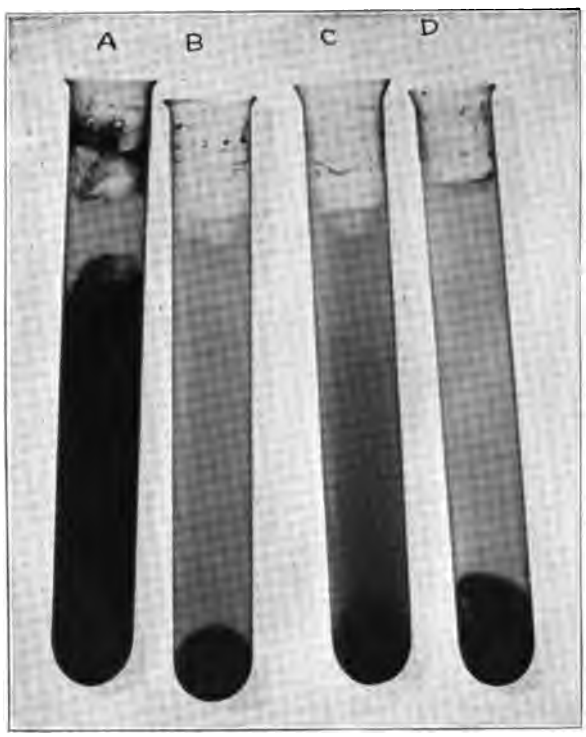

Fig. 17.—Roentgenograph of same tubes and materials as shown in Figure 16, at the end of sixteen hours. An equal quantity of bismuth was placed in each tube.

esophagus. By swallowing various sized pills the size of the opening can be determined.

If the patient is given one big swallow of the bismuth-kefir mixture, it drops quickly to the lower third of the esophagus and here, in normal subjects, it requires about seven seconds for it to pass into the stomach. The retention here is probably due to a sphincteric closure of the cardiac orifice, which only allows the liquid to pass in slowly.

While the bismuth-kefir food is resting in the lower third of the esophagus, it may be seen to fluctuate rhythmically with the pulsations of the heart. There is also an active peristalsis at this point, which is best observed in stenosis of the cardiac orifice, such as I observed in a syphilitic stenosis, when two capsules could be seen churning about each other.

I have observed two cases of malignant stenosis of the cardiac orifice. One was in a man aged 60, who was referred by Dr. Daland, and in whom I found a dilatation above the cardiac orifice of about two inches. The second case was a woman of 65, referred by Dr. W. E. Robertson. She had almost complete obstruction, and I found that the esophagus retained about ten ounces of the bismuth-kefir mixture. This produced a shadow about two-thirds of the size of the heart, and was in reality about one-half the size of the heart. The esophagus is dilated from the bottom up.

I have had one case of syphilitic stenosis of the cardiac orifice in a colored boy of 22 years of age. The degree of stenosis varied with the regularity with which he took the specific treatment. It varied from the distinct obstruction to the passage of the bismuth-kefir mixture to the free passage of a large capsule and beefsteak.

A fourth case referred by Dr. Arthur H. Cleaveland showed a tumor mass just below the level of the cricoid cartilage, which caused obstruction to the passage of any solid food.

A fifth case of esophageal obstruction was a man of 72, referred by Dr. Alfred Hand. In this patient we could observe the esophagus, without rendering it opaque by any artificial means, from a level with the arch of the aorta to the cardiac orifice. There was evident general thickening throughout, which Dr. Hand believed to be due to a caustic solution swallowed early in life. There was a distinct obstruction to the passage of food of any kind at the level of the arch of the aorta and at the cardiac orifice.

In four of these cases I tried to record the picture on the photographic plate, but on account of the oblique position the shadows are very irregular and difficult to recognize. For this reason I have made a tracing directly from the negatives (Fig. 18).

In general, it will be seen how great will be the value of this method of examination in differentiating obstruction due to pressure from aneurism, tumor or enlarged glands from without and obstruction due to growth within. It also enables us to decide the exact and relative location of the growth and its size and extent.

THE STOMACH.

The technic to be used in the examination of the stomach will vary with the object to be attained. For most practical purposes the standing posture will give us the desired information. Holzknecht describes in great detail the technic necessary to study the stomach in various positions, but adds that it is seldom necessary to use all of these positions in the study of any one patient. Therefore, most of my work, but not all, has been done with the patient in the standing posture. Ordinarily, the tube is placed back of the patient and the screen or plate anteriorly. The anode of the tube is placed perpendicular to the center of the screen. Then any part of the patient brought to the center of the screen will be in an orthodiagraphic position and the shadow will not be in any way distorted. In this way any desired point about the stomach can be accurately determined and marked on

the glass covering the screen or on the skin of the patient.

For practical work I place a coin over the umbilicus and one over the tip of the ensiform cartilage. I then bring the tube and the center of the screen to a point midway between these two marks. The screen is 24 inches from the anode of the tube, and the skin of the patient against the screen, therefore, there will be less than one-

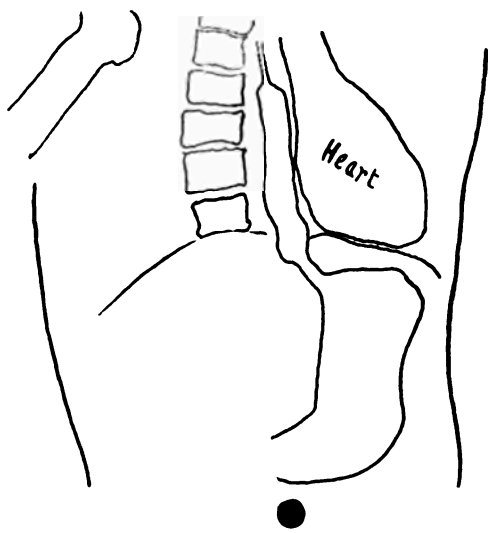

Fig. 18.—Tracing of Roentgenograph showing esophageal stenosis.

half inch error at either pole, and a half inch will not change the diagnosis.

The greater curvature will at once be visible and by slightly rotating the patient to the left the lesser curvature will appear. Ordinarily the lesser curvature is obscured by the shadow of the spinal column. It is well to note the lower pole of the stomach when empty by giving only a small quantity of the bismuth-kefir mixture (bismuth subnitrate one ounce and kefir one pint) one-half to one ounce.

This is seen to enter at the right side of the fundus of the stomach which is marked by a light area, just below

the diaphragm, which indicates a collection of gas in the stomach. It appears like the moon breaking through the clouds. The bismuth food is seen to pass along the right and lower or inner side to the bottom of this collection of gas which now assumes a funnel shape, and gradually or within a few seconds the food is seen to pass downward in a small stream curving slightly to the right after it reaches nearly to the umbilicus, and at this level spreads out again into a broader area. This will mark the lower pole of the stomach when it is empty. Often when the stomach is only partially filled it suggests an hour-glass contraction, even though normal, and at times in cases of gastroptosis, but this illusion is immediately dispelled when the stomach is filled. If the hour-glass constriction remains when the patient has taken all of the food possible, then it is almost certainly due to organic constriction.

The walls of the upper half of the stomach can be directly observed by distending it with gas. This may be accomplished by allowing the patient to drink alternately small quantities of solutions of bicarbonate of soda and tartaric acid. By taking it slowly the degree of distension is under perfect control, and should cease when the patient complains of the slightest discomfort. A more simple way is to allow the patient to take the bismuth-kefir mixture in very small swallows. In this way he swallows a quantity of air equal to about one-half the quantity of the bismuth-kefir mixture. By either of these methods it is possible to overdistend the stomach and cause fainting, as occurred in two of my patients, one with the effervescing solutions, and one in which the stomach was distended by allowing the patient to swallow air with the food. As soon as this gas is expelled, which occurs in a few minutes, the patient is again comfortable.

The lower half of the stomach is best observed by distending it with the bismuth-kefir mixture. The out-

line of the walls as studied in varying positions should then be noted, and finally the changes that take place during the process of digestion and the effects of massage, respiratory movements, and the effect of the contractions of the abdominal walls should be noted.

THE INTESTINES.

The small intestines can only be studied by tracing the food from the stomach. Unless there is some obstruction or lack of peristaltic action, little can be seen of the food during this course, because it is distributed over a long canal and, therefore, in small quantities, and because the food moves so rapidly. The food often passes from the pylorus to the cecum in six hours or less. In fact, in one of the healthy subjects examined the food was in part passed from the rectum in four hours from the time it was taken. This occurred in a medical student and was probably hastened by the excitement and interest connected with the examination.

The colon is most conveniently studied by following the food from the stomach and small intestine. Usually it will be found distributed through the colon in twenty-four hours after ingestion. Bismuth food may be introduced by rectum. It is best to allow the patient to rest first on the left side, then occupy the dorsal or the knee-chest position, and then lie on the right side. These positions will hasten the distribution of the food, but it will also be carried upward by the reverse peristaltic movements.

When a new growth is to be outlined, either in the colon or adjacent to it, air should be injected into the colon slowly by means of an atomizer bulb attached to a soft rubber catheter. This will often give great assistance in differential diagnosis.

DISCUSSION.

DR. J. DUTTON STEELE, Philadelphia, said that most of the *x*-ray photography in gastric and intestinal disease has considered only the topography of the various organs and the change that takes place in their position and size. This paper

enters the much more important field of morbid physiology and attempts to determine not only the anatomic changes in disease, but disturbances of motility as well. He stated his belief that the study of the gastrointestinal tract by means of the *x*-rays will develop along these lines and will aid in solving many obscure problems. It has become the fashion, he said, to ascribe many gastric symptoms to disturbances in gastric motility, and especially is this so of various indefinite sensory disturbances which were formerly ascribed to changes in gastric secretion. After it was found that the effects on the stomach of alterations in the gastric acidity had been greatly overestimated, physicians were liable to explain such changes in sensation by assuming that they are caused by atony and gastric motor insufficiency of minor grades. Particularly is this so in gastroptosis. All recognize that downward displacement of the stomach does not in itself cause symptoms, and that some important factor besides ptosis must be present before there is marked disturbance of the function of the stomach. Dr. Steele thinks that most observers believe that this factor which determines the presence of symptoms in cases of gastroptosis is gastric motor of insufficiency of more or less minor grade. This idea is a very natural one for several reasons:

1. The pyloric end of the stomach is the part that sinks and the cardiac end remains against the diaphragm. In many cases this causes an apparent kink in the pyloric end of the stomach and appears to cause a similar kink in the duodenum. This has been shown by *x*-ray pictures. Whether this kink is enough to cause serious obstruction, he believes, is open to doubt, but at all events it is the most striking thing one sees in *x*-ray pictures of enteroptosis, and it is natural that considerable emphasis should be laid on it by observers seeking an explanation for the causation of symptoms in gastroptosis. That there is the disturbance of gastric motility in many cases of gastroptosis Dr. Steele did not deny, but that gastric motor insufficiency and retention can be assumed as present in every case of gastroptosis with symptoms is, he thinks, very doubtful. 2. It is undoubtedly true that in many cases of gastroptosis the stomach empties itself in a shorter time than usual. This has been observed by many writers. 3. The movements of the stomach are very complex as shown by the work of Cannon and others. Physicians speak of the organ when discussing gastric atony as if its only function were to hold the food until sufficiently digested and then to empty it into the duodenum. But when it is considered how the food is mixed and churned in one portion while it lies without movement in the cardiac end, and how intricate and selective is the mechanism of the opening of the pylorus, it is seen that the mechanism is very much more complicated than the earlier and simpler conceptions of gastric

physiology have led us to believe. 4. There is no reliable method of determinig changes in gastric motility, particularly those of minor grades. Decided retention of food can be demonstrated by washing out the stomach four or five hours after a test meal, but none of the methods of determining motor disturbances of lesser degree as those suggested by Sahli, Elsner, Mathieu and Raymond have stood the test of experience and time.

When all these points are considered, it seems to Dr. Steele that physicians must acknowledge that they do not know enough of the motor mechanism of the stomach and its variations in disease to assume that the symptoms of disturbance of gastric function in cases of gastroptosis are due to gastric atony alone, especially as in some cases there is hypermotility instead of motor insufficiency. It is in the solution of these obscure problems that *x*-ray photography can aid in determining in the human subject what Cannon has done to some extent in animals, namely: 1. To determine the normal function of the stomach. 2. To determine the morbid physiology of gastric motility and its clinical significance. In conclusion Dr. Steele said that in his opinion the solution of the vexed problem, Why symptoms are present in some cases with gastroptosis and are not in others, is this: Ptosis of the stomach makes it, for some reason, a point of lesser resistance and when there is a general lowering of nervous strength in the individual, the stomach is the place where the general loss of nerve power first manifests itself. As a consequence, there are various forms of gastric neurosis, motor, sensory, or secretory. When by treatment directed to raising the nervous energy of the individual as a whole, this gastric neurosis is relieved, the stomach symptoms cease, although examinations will show that there has been no change in the position of the stomach as a result of treatment.

Dr. L. C. Grosh, Toledo, Ohio, said that gastroptosis frequently occurs in the symptom complex called neurasthenia. In this condition the dilatation can be looked on as a sign of depression of the function of tonicity of the muscaluture of the stomach wall. It is frequently associated with dilatation of the heart due to the depression of this function. Dr. J. Mackenzie, England, called his attention to a number of cases of gastroptosis recurring during the cold months of the year, these were associated with undue coldness of the hands and feet, cardiac dilatation and inspiratory increase of the amplitude of the jugular pulse.

Dr. James M. Anders, Philadelphia, regarded the paper of Dr. Pfahler as being not only interesting but very valuable for diagnostic and thereapeutic reasons. He confirmed what was said in reference to the size and position of the normal stomach, thanks to the courtesy and privilege given him to see these cases during the examination. All physicians know

that in a number of instances of gastroptosis there are no symptoms; but up to the time Dr. Pfahler made his demonstrations and explanations, the subject was not so clear. Dr. Pfahler has shown that the process can be watched carefully during an *x*-ray examination and that there may be a gastroptosis and yet good stomach motility. So long as the stomach has this motility, just so long will there be an absence of symptoms; this ocular demonstration is of more value and gives better satisfaction than any attempted explanation for it. Dr. Anders is sure that this method will substitute the old ones of investigation into and study of the motility of the stomach; not only this, but the time required for the passage of the food through the intestines, and each physiologic section thereof can be accurately determined by this method. In one of the cases studied by Dr. Pfahler, points of obstruction were found at two different places. The *x*-rays also throw light on the nature of the obstruction in some cases at least. This was true of the case referred to above, in which the impediment was of a transient or spasmodic character. Dr. Anders said that he had had the privilege of observing every advance made by Dr. Pfahler for the cure of gastroptosis, and he is sure that by strengthening the abdominal walls, or the abdominal muscles, through special physical exercises and other agencies, the condition can be overcome successfully. He referred to a case, in a young lad, who came to him with a gastroptosis of moderate degree; there was also a descent of other viscera. After studying the case with Dr. Pfahler his diagnosis was confirmed. There was a history of constipation almost from birth, for which every method of treatment had been tried. As the result of two months treatment, when the lad was re-examined by the *x*-ray, it was found that the stomach had moved upward a distance of at least two inches as compared with its position at the first examination. In that case, the most remarkable thing was the result of rearranging the diet; this in connection with the physical exercises that were instituted, and the outdoor life, resulted in regular bowel movements without the use of laxatives. The theory advanced by Dr. Pfahler to explain the phthisical thorax needs further confirmation. Doubtless Dr. Pfahler has cured some patients by elevating the stomach by strengthening the abdominal muscles, which re-expands the chest and overcomes the phthisical thorax, but recognized causes are for this condition. Dr. Anders has often found that the phthisical thorax so-called, is a result rather than the cause of pulmonary tuberculosis. It may be due to mere delicacy in the patient's constitution. Therefore, in such cases, other modes of treatment must be instituted. Dr. Anders feels strongly that a new era is approaching in the study of gastrointestinal diseases by the *x*-ray.

DR. JUDSON DALAND, Philadelphia, said that in his opinion the most important points in Dr. Pfahler's paper are: First, the use of the admixture of bismuth and kefir, by which means the bismuth remains in suspension sixteen hours. Second, the utilization of the important and original observation in the fluoroscopic and radioscopic examination of the intestinal tract. Another point of interest is the ocular demonstration and measurement of the amount of gastroptosis and enteroptosis. A matter of equal importance is the demonstration of the relationship of the abdominal wall to the abdominal contents. When the wall is abnormally relaxed, the abdominal contents move downward and forward. In gastroptosis, extreme contraction of the muscles of the abdominal wall causes the stomach to ascend from two to six inches. In ordinary gastroptosis, the stomach returns to its normal position in recumbency. The standing-up exercises, so popular in military circles, are of particular value in correcting stoop shoulders, a condition of the normal vertebral curves and protuberance of the abdomen. When coupled with graded and systematic exercises designed to strengthen the abdominal muscles, the beneficial effect on the position of the abdominal contents is truly remarkable. These points Dr. Daland considers of extreme significance, not because they were not known heretofore, but because they have been made visible. The question of motility of the stomach is an important one and he believes that the explanation given, i. e., that displacement of the stomach and intestines without symptoms may be detected when associated with normal motility, is the true one, but he also believes that there are other explanations. It is very interesting to watch the movements of the stomach during the movements of the diaphragm, the beautiful slow, rhythmic and swaying movements that are observed during the ascent and descent of the diaphragm are most instructive, but impossible of adequate verbal description. Dr. Daland believes that duodenal obstruction, by kinking, plays an important rôle in certain obscure cases.

Dr. Daland has witnessed the results of swallowing six ounces of bismuth and kefir in a case of esophageal obstruction due to cancer of the cardiac end of the stomach. As soon as the mixture arrived at the obstruction, the esophagus slowly dilated forming an elongated triangle with the base downward, with a capacity of six ounces, forming a small secondary stomach which subsequently delivered its contents into the true stomach. In a normal individual, when the stomach is distended with gas and bismuth-kefir mixture is swallowed the mixture can be seen entering the stomach in a continuous tiny stream. Dr. Daland said that this valuable contribution of Dr. Pfahler makes possible the diagnosis of certain diseases of the alimentary tract in which hitherto diagnosis has been impossible or conjectural, and in other

cases demonstrates a diagnosis already made and gives much additional information. Having observed many of the cases on which Dr. Pfahler bases his conclusions, Dr. Daland vouches for the accuracy of the work and the correctness of the deductions. He furthermore believes that the study of any serious or chronic affection of the alimentary tract is incomplete if *x*-ray examination is omitted.

DR. ALLEN A. JONES, Buffalo, N. Y., said that members of the profession have been familiar with the disease known as gastroptosis and, in a therapeutic way, have for years practiced as best they could the measures that would, or should, increase intraabdominal pressure, and strengthen the tone of the abdominal muscles, by exercises, etc. Until the *x*-ray came into use, however, it was not possible for them to observe the exact position of the stomach before and after treatment, nor was it possible to observe the exact movements of the stomach and intestines as done by Cannon, Pfahler, and others. Dr. Jones some years ago declared that, in his opinion, this condition commences early in life in not a few instances; it commences, he said, in childhood and finally develops into a pronounced gastroptosis. This is the result of several factors. Frequently we see this condition in children who are run down and in school, and in those who are liable to go without advice as to their diet and especially the amount of food they should eat. The rapid overdistension and overloading of the stomach common in children initiates gastroptosis. That is a more important factor in its causation than is generally assumed. Added to these factors fatigue of the stomach is a cause and that there are not more cases is due to the fact that all people are not constituted alike. The question of atony in gastroptosis is important, as the condition invites atony and predisposes to it. If atony does not exist early in gastroptosis as the nutrition suffers it will necessarily follow. In the treatment the general condition of the patient should receive attention in the endeavor to make him stronger; but it is a difficult matter to do this. The abdominal muscles may be exercised, but until the metabolism of the patient is such that nutrition is possible it is impossible to improve the state of the abdominal muscles or the gastrointestinal musculature. The most brilliant results follow not from the exercises, he asserted, but from the rest treatment. These patients should receive careful abdominal massage in the prone or inverted slanting posture, and electricity should be applied to the abdomen. They will improve, gaining sometimes, many pounds in weight. The possibility of this great gain results not from the exercises, but from some peculiar and wonderful influence on the nervous system that promotes the nutrition of the body.

DR. J. C. JOHNSON, Atlanta, Ga., said that unless he has made mistakes in diagnosis he believes that he has cured a number of patients with gastroptosis. He is sure that he has seen a stomach displaced below the umbilicus in very emaciated patients whose weight was reduced almost one-half; he has seen it in several instances and he is bold enough to say that there was no doubt about the diagnosis. The *x*- ray was not used to make the diagnosis. There was the splashing sound and the distension from inflation, and other signs which left no doubt about the correct diagnosis. He examined one patient recently and the stomach was found to be in the normal position; this patient instead of weighing 91 pounds now weighed 164. This was nine years since the diagnosis of gastroptosis was made. He believes that the configuration of the body and the height should be considered in making a diagnosis of gastroptosis. He believes that motility of the stomach is more important than its position, and that ptosis of the stomach may exist and yet the motility be so increased that the patient may enjoy good health. There is no doubt about the ascent and descent of the abdominal organs in respiration; if anyone doubts, and wants to determine this point, let him, in cases of gastroptosis, take hold of the abdominal wall and pull up and see the chest elevate; it is remarkable how much effect this has and shows well the physical relation between the thorax and the abdominal organs. He has great faith in intragastric faradism, and he also endorses the use of the band. He said that his main object in discussing this paper was not only to express his appreciation of it but to say that he believes that in the great majority of the cases of gastroptosis in which the stomach can not be restored to the normal position, it can be so improved that the condition is hardly recognizable.

DR. JOHN A. LICHTY, Pittsburg, said that he had followed Dr. Pfahler's work, but he has not had my patients examined by his method. The men who do this work told him that it requires a particular kind of tube, one of high intensity, and that the examination is a very expensive one, and they do not like to subject the patient to such an expense of this kind unless it is absolutely necessary. Only in exceptional cases is this method of examination necessary. During the past three years he has elaborated a method for determining the position of the stomach by auscultatory percussion which is very satisfactory. He mentioned this merely for the sake of those who are not willing to subject their patients to such an expense and who have not these facilities. One principle is involved in this method which must not be lost sight of: no matter how low the stomach will drop, the esophagus still extends up to the mouth and must pass under the left costal margin. The physician should first percuss over the left

costal margin and notice the tone or note heard there; then he should bring a heavy phonendoscope, which need not be touched to hold it in place, down over the abdomen toward the umbilicus, by remembering the note it can be heard further down. Percussion can be continued over the costal margin noting the place where the same tone is heard. Dr. Lichty worked for years with this method before he gained confidence in it. In a large number of cases the true position of the stomach will be found by this method. He recently had a case in which he was doubtful of the method, in differentiating between a dilated colon and a prolapsed stomach. The splenic flexure of the colon may be high while the other portions may be low and dilated; one is easily mistaken in such cases. In the case he referred to, he dilated the stomach with air and confirmed the diagnosis with the stethoscope. When the laparotomy was performed the stomach was found exactly where he had mapped it by percussion and with the heavy phonendoscope.

Dr. Woods Hutchinson, New York, declared that there is a great difference in the condition of affairs in the elevated or erect position and that found after death in the dorsal decubitus. He said that he regrets that this study had not been carried a little further in order to confirm or to disprove conclusions that arise. Cannon's case in which the stomach had two pouches instead of a single one was curious. Dr. Hutchinson became convinced of the possibility of this condition several years ago by his studies of comparative anatomy. The central band of circular fibers of the pyloric antrum contract and shut off the acid region of the pylorus when active digestion takes place, and the food may remain alkaline in the other portion hours after it has been swallowed. Again, as Cannon states, there is a difference in the motility of the stomach and the rapidity with which the food is passed on according to the character of the food. Experiments made with milk showed that it passes on almost immediately and the size and the shape of the stomach differed greatly when a mixture containing starches was given. Dr. Hutchinson said that physicians had been in error in thinking that milk is easily digested because it gets out of the stomach quickly. He also spoke of the tendency to regard gastroptosis as a diseased condition. It is nothing but a symptom, he asserted, and should be so regarded. He believes that all who have seen a number of chronic invalids in sanatoria will testify that from one-half to two-thirds of the number have gastroptosis. The condition is very prevalent in tuberculous patients. He regards the military set-up drill as a ridiculous exercise in these cases; it is an exaggeration of the erect position, and diminished the tonicity of the abdominal muscles. No prize fighter would assume that

position excepting to protect himself by contracting the abdominal muscles; he takes the crouching position, and this is, Dr. Hutchinson said, more beneficial in developing muscular tone. He protested against placing movable organs in splints; no good results from permanent bandaging in these cases, though there may be temporary relief. These patients should be toned up generally by the rest cure and improved nutrition, as Dr. Allen Jones said. So soon as the bandage is removed, the abdomen relaxes again and the patient is no better than before.

Dr. G. E. Pfahler, Philadelphia, repeated the statement made in his paper, that the bandage only acts temporarily in order to enable the patient to be relieved of the symptoms long enough to gain nutrition and strength to support the abdominal contents. In regard to exercise, of course every physician realizes that each patient must be dealt with as a patient, and not according to rule. The abdominal walls should suport the abdominal contents; when that support is gone, the object of treatment should be to replace that support. He said he had not carried on his investigations as to the kind of food necessary, so far as he would like, because of the lack of time. He did not report in his paper one-half the work he has done and he intends to carry on investigations with other kinds of diet.

OBSERVATIONS ON PLAGUE IN INDIA.

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PHILADELPHIA.

Plague, in the time of Galen, was any epidemic disease causing many deaths, but the word is now restricted to that acute epidemic, febrile disease, with polyadenitis, due to the plague bacillus. It is believed to be transmitted to man by fleas that have infected plague-stricken rats. This malady has doubtless existed for ages, and certain epidemics that occurred two or three hundred years before Christ were unquestionably plague.

In the fourteenth century plague was pandemic and spread from the tropical and subtropical countries of the East through Europe as far north as Greenland, and it is estimated that the mortality was in the neighborhood of 25,000,000. Between 1876 and 1889 it is estimated that more than 250,000 deaths occurred from plague. This disease is now confined to Asia and is only occasionally imported into Europe by way of Turkey. The following centers for this disease are recognized: (1) Bombay, (2) Uganda, (3) Persia, (4) Thibet, (5) the west coast of Arabia, and (6) eastern Siberia, in all of which plague is always present, either sporadically or endemically, and from these centers epidemics and pandemics originate.

The plague bacillus was discovered by Kitasato and Yersin in Hongkong in 1894. It is a short, thick bacillus resembling that found in chicken cholera, having a length of from 1.5 to 1.75 microns and a breadth of

from 0.75 to 0.7 microns; it is ovoidal, slightly convex, rounded at each end, non-motile, aërobic and frequently appears as a diplobacillus which occasionally joins, forming short chains. This new organism takes a characteristic bipolar stain with methylene blue, the middle portion often remaining transparent. During life the bacillus is easily obtained from the bubo in the bubonic, from the sputum in the pneumonic and from the blood in the septicemic forms, and after death may be discovered in almost all the tissues. The following varieties are recognized clinically: (1) Bubonic, (2) pneumonic, (3) septicemic, (4) intestinal and (5) ambulatory. The vast majority of cases fall under the first group. The septicemic form is rare as a primary affection, but is not uncommon in the terminal stage. The ambulatory form is most active in the spread of the disease, as the symptoms are so slight as to cause but little inconvenience and, therefore, seldom come under medical observation.

One of the first cases of pneumonic plague diagnosed during life was that of Maj. Manser, who was one of the faculty of Grant Medical College in Bombay and who was under the care of Maj. Childe, the present incumbent of the chair of medicine in that institution. He presented the ordinary signs and symptoms of pneumonia. As extreme prostration showed itself early, Maj. Childe suspected the pneumonic form of plague, and the sputum, by staining and culture, showed the plague bacillus. The patient was in good health January 2 and died January 6. The nurse who attended him fell ill on the following day and died three days later of the same affection. There was no dyspnea nor the ordinary pneumonic disproportion of pulse and respiration; the sputum was a pinkish serum and bore no resemblance to the characteristic rusty sputum of pneumonia, and the general condition was far worse than could be explained by the small amount of lung involved.

My personal experience with plague includes about 50 cases observed in the Maratha Plague Hospital in Bom-

bay during the summer of 1905. This hospital is especially devoted to plague, although it is occasionally necessary to set aside pavilions for other diseases, such as relapsing fever, etc. The hospital is composed of a number of pavilions, one story in height, with beds made of wood, the bottoms of which are covered with rattan. These beds are placed on each side of the pavilion and number about 20 or 30. Contrary to our custom the patient faces the window. The total capacity of the hospital is about two or three hundred, and in times of epidemic, by overcrowding, the capacity is doubled. No attempt is made to make bedside notes, and all records are placed on the temperature charts, which show the name, age, date of admission, temperature, and only occasionally the pulse and respiration. A record also is made of the day of the disease and the treatment. Blue and red pencil marks are used freely for any additional data.

These pavilions are thoroughly well ventilated by numerous windows and doorways. The native habitually keeps his head covered by a sheet, which strange custom is probably due to the fact that he is accustomed from childhood to covering his head with a thick turban, which renders the head peculiarly sensitive to drafts and slight changes of temperature when the head covering is removed. This sensitiveness is still further accentuated by the custom of wearing the turban during the entire day and evening, excepting when eating or sleeping. The natives occasionally utilize this strange head covering at night as a pillow, and at all times it serves as a bank, as money may be discovered tied in one corner of the material composing the head dress.

Patients with plague are transferred to the hospital by means of a two-wheeled vehicle, on the top of which is placed a stretcher. This ambulance is painted white and is in charge of two men who supply the motive power. The patient is covered by a coarse blanket, and it is the belief of the physicians of Bombay that these patients do

not propagate the disease while being transferred from their homes through the narrow crowded streets to the hospital.

The expectoration in primary pneumonic cases is infective, and it is believed that the urine may possibly carry this disease, but the discharges from the bowels are believed to be free from this danger. Suppurating buboes are often highly infective, and in acute cases the pus from these buboes show large numbers of plague bacilli.

The hospital is under the direction of Dr. N. H. Choksy, assisted by a native physician. Dr. Choksy is possessed of unusual vigor, both mental and physical, and is the happy possessor of an intense enthusiasm and love for his work. He is, however, handicapped by duties which belong more strictly to a superintendent, which duties occupy time which should be spent in purely medical work. He has been in close association with plague for many years, and to-day probably possesses more practical information regarding the clinical aspect of plague than any physician in Bombay or elsewhere. The Parsees, followers of Zoroaster and worshipers of fire, although few in number, are remarkably intelligent, prosperous and charitable, highly neurotic and differ widely from the other nations of Bombay and possess many of the mental and emotional characteristics of the better class of Hebrews. Special pavilions are assigned the Parsees in the Plague Hospital, which custom is followed in other public institutions. They visit their sick at all hours and in such numbers as seriously to interfere with their proper management and nursing.

The Maratha Plague Hospital and the Arthur Road Hospital are so rich in clinical material illustrating various contagious diseases more or less peculiar to India that it is regrettable that each medical student in Bombay is not compelled to live a certain number of months with these patients. Most of the cases of plague present the ordinary features of the bubonic form of the

disease, but few show the septicemic or pulmonic variety. The latter occurs in about 0.5 per cent. of all the cases, although terminal pneumonia is present in about 10 per cent. of the cases. When bacilli are found in the blood 98 per cent. of the cases are fatal, and many patients enter the hospital and die before the medical officer's visit the following morning. Most patients, however, die on the third day, and the average daily mortality among the natives is 81 per cent. and among Europeans about 15 per cent.

When plague is complicated with tympanitis it is usually fatal, and when the thyroid is affected it constitutes a grave complication. The common complications of plague in the order of frequency are:

1. Delirium.
2. Cardiovascular weakness or paralysis.
3. Tympanitis.
4. Persistent vomiting and diarrhea, which are rather uncommon.

The rarer complications are:

1. Aphasia.
2. Peripheral neuritis.
3. Bulbar paralysis.
4. General acne resembling chickenpox, which may appear in one night.
5. Panophthalmitis followed by total blindness, which may occur within twenty-four hours.
6. Keratitis.
7. Hematuria, which was rather common in the last epidemic.
8. Meningitis.
9. Secondary pneumonia.

In one case of plague at the end of the fifth week the classic symptoms of meningitis developed. The following combination of diseases are occasionally met with during epidemics of plague: (1) Plague and smallpox; (2) smallpox and plague; (3) relapsing fever and plague, in which case the fever chart shows a less marked crisis, but the buboes suppurate, as is usual in plague; (4) plague and relapsing fever; (5) relapsing fever

chickenpox and plague; (6) plague and measles, in all such cases the mortality is very high; (7) erysipelas. leprosy and plague; (8) leprosy, smallpox and plague.

Each of these mixed infections are exceedingly rare. In fourteen hundred cases of plague but three of smallpox and plague were observed. When a case of plague occurs complicated by epistaxis it suggests the possibility of the coexistence of relapsing fever, and when subnormal temperature and perspiration also are present examination of the blood will show the presence of the spirillum of relapsing fever. Occasionally errors in diagnosis occur, of which the following is an example: A patient entered the hospital suffering from fever, bubo and pain over the bubo, particularly on pressure. During an epidemic of plague these symptoms are usually sufficient to make a diagnosis of plague. Two such cases occurred in men sent from a jail in Bombay. Examination showed that the bubo was an old enlarged gland and that the skin overlying was hyperesthetic. The blood examinations proved that they were cases of relapsing fever and not plague, and many hundreds of inmates of the jail were later seized with this malady.

The number of cases of plague in India during the summer of 1905 was comparatively few and many of the pavilions were empty. I observed in the neighborhood of fifty cases, however, all occurring in natives. The average daily mortality in Bombay was forty; during an epidemic it rises to one or two thousand. Many die in their homes without medical attendance. The majority of patients were ill two or three days prior to their admission to the hospital. The vast majority of the cases were of the bubonic variety and the glands usually affected were the inguinal or femoral, the axillary or cervical, and there was one example of primary involvment of the isthmus of the thyroid.

Not infrequently the inguinal or axillary or the inguinal and cervical would be affected in the same indi-

vidual. In the majority of cases the diagnosis was based on: (1) Sudden onset; (2) extreme prostration; (3) fever, which usually decreased on the third day; and (4) painful glandular enlargements or buboes. In no instance was the diagnosis corroborated by the discovery of the plague bacillus. Clinically the introduction of a hypodermic needle into an enlarged gland and the removal therefrom of a small quantity of lymph in which the pest bacillus may be recognized, establishes the diagnosis in doubtful cases. Unfortunately the natives object to autopsies and it is the policy of the government to acquiesce so as to popularize the hospitals. In consequence no autopsies have been performed in the Maratha Plague Hospital for more than four years.

As a rule the onset of plague is sudden as if the patient was "stricken down," and although diarrhea is uncommon, it has been observed before death and is colliquative in character. The washed-leather appearance of the tongue is diagnostic.

The following is the report of two cases of plague, one occurring in Dr. N. H. Choksy and the other in his father-in-law.

Case of Dr. N. H. Choksy:—The attack began on the morning of May 7, 1904, the axillary gland showing enlargement, probably from an infection received through a small blister, which was unopened, situated on the tip of the left index finger. The temperature rose in a few hours to 106 F., accompanied by delirium. There was considerable periglandular inflammation and edema and the bubo was only moderately painful. The first two injections of the Roux serum were 100 c.c. each and subsequent injections were smaller. On the first day two injections were given; on the second day two and three injections were given, subsequently and in all 400 c.c. were administered. Ordinarily 100 c.c. repeated thrice, at six-hour intervals, are sufficient to abort ordinary cases of plague. Four hundred c.c. of serum were injected around the bubo and one injection was given on the opposite side. The temperature descended to normal on the fourth day. Afterward there was an interval of five or six days during which time he was in good health and then fever occurred with urticaria, an after effect of the serum. This urticaria affected

both upper extremities, which became extremely red, many wheals formed and itching was extreme. Later a third rise in temperature ensued with pain and swelling, one after the other, of almost all the joints of the body, the wrists, elbows, shoulders, hips, knees, ankles and maxillæ. These joint phenomena were secondary to the serum. During the third week severe neuritis accompanied by spasms occurred, chiefly affecting the thighs and legs. The least movement was agonizing. Morphin and atropin were useless. Improvement was eventually secured by the use of opium, which was spread all over the limbs, which were bandaged afterward with cotton. He remained drowsy for three days. Spasms, weakness of the limbs and wasting of the muscles caused great suffering for four months. Although right-handed, the muscles of the right forearm are less in bulk than those of the left. In five months he was able to begin work, but it was necessary to move with great caution as the slightest over-use of the muscles immediately induced spasm. Lithicin in two-grain doses, four times a day until 200 grains had been taken, improved the tone of the muscles, lessened pain and increased weight. Occasionally the glycophosphites act beneficially in the nervous troubles following plague. Moderate fever was produced by nervousness and suffering and his medical adviser ordered suppositories containing quinin, which produced proctitis with retention of urine, to alleviate which a rubber catheter which unfortunately was unclean was passed and was followed by cystitis. Following the proctitis, hemorrhoids, from which he had occasionally suffered, became acutely inflamed and rectal hemorrhages frequently occurred during a period of two months and almost caused death. Relief was secured by a complete change in diet, as drugs were valueless.

Case of Dr. Choksy's Father-in-Law:—The patient was infected May 1, 1905. Returning home from business at 7 p. m., he felt sick with slight pain in the groin. He was able, however, to take dinner as usual, and had none of the premonitory symptoms described by Hunter. As the pain in the groin increased and fever appeared, he lay down. At 9 p. m. the temperature was 101 F. and the pulse was rapid. He declined medical assistance, feeling that it was unnecessary, but in one hour, i. e., 10 p. m., the temperature had risen one degree. At 10:30 p. m. he was given 100 c.c. of serum and the following morning another 100 c.c., and at 4:30 p. m. a third injection of 100 c.c. In spite of these injections a bubo appeared on the opposite side, showing the malignancy of the infection. After the third injection the temperature fell and on

the morning of the third day became normal. On the fourth day two injections of 50 c.c. each were given as a prophylactic and the buboes rapidly declined in size and he made a good recovery.

While I was in Bombay the plague commission was engaged in successfully solving the question of the transmission of plague; preliminary communications have already appeared in print and further reports will soon be published. Their experiments prove that fleas from rats dead of plague are able to transmit plague to rats, guinea-pigs and monkeys.

By an ingenious method devised by Captain Liston infected fleas were secured by placing a live guinea-pig in a room in which plague had occurred. Although a rat flea will not by choice select another animal as its host, under the influence of hunger it will attack almost any living animal. A cage of healthy rats surrounded by a fine wire gauze, when placed in a room from which patients dead of plague had been removed, remained free from plague, whereas the majority of rats, exposed in a similar manner, unprotected by wire gauze, died of plague. When rats imported from England were thus exposed they all died of plague, which suggests that a certain proportion of Bombay rats are immuned to this disease. Complete protection of healthy rats, when confined in an ordinary wire cage and placed in an infected room, was secured by suspending the cage in the air or by placing it on the floor, provided it was surrounded by a strip of fly paper wider than a flea could jump. Infected fleas secured by the live guinea-pig method, when permitted to attack healthy rats, guinea-pigs or monkeys in flea-proof cages, caused an epidemic of plague among these animals. The discovery by Captain Liston of the rat flea on the body of a Hindoo dying of plague adds one more link to the chain of evidence tending to prove that the infected flea from the plague-stricken rat is the transmitter of plague from the rat to man. It will be most interesting to learn the precise

manner in which this transmission occurs and the behavior of the *Bacillus pestis* while in the body of the flea.

For many years the natives of India have been convinced of the necessity, during epidemics of plague, of (1) evacuation of villages when disease and death appears among rats; (2) burning the houses of the villagers; (3) destroying the roofs of houses so as to permit the sunshine to penetrate all portions of the dwelling, as the flea prefers darkness. The correctness of this belief is easily comprehended in the light of the results secured by the plague commission, as is also the cause of the infrequency of plague among Europeans.

It is regretable that the time allotted to this communication forbids a discussion of sanitary and quarantine questions, the present status of the treatment of plague by sera prepared in accordance with the methods of Prof. Lustig of Florence, Prof. Terni, formerly of Messina and now of Milan, and Dr. Brazil of San Paulo, Brazil. Consideration should have been given to the efficiency of adrenalin, spartin, caffein, the uselessness of alcohol and the undoubted value of Haffkine's serum as a prophylactic in plague.

OPSONINS AND THE PRACTICAL RESULTS OF THERAPEUTIC INOCULATION WITH BACTERIAL VACCINES.*

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TORONTO, CANADA.

No subject of recent years has been before the medical world more prominently than the opsonic theory and inoculation with bacterial vaccines, and we must earnestly consider whether or not such an interest is justified. To reach a right conclusion we must view the whole subject from at least two standpoints: the one is that of the opsonic theory and the other that of the therapeutic inoculation with bacterial vaccines. Let us first review very briefly the theory and then devote most of our attention to the results achieved by inoculation with vaccines.

Opsonins are substances not yet isolated, but known to exist in the blood, whose function it is to unite with bacteria and prepare them for the leucocytes to attack and destroy. Without such preparation the fastidious leucocytes refuse to ingest bacteria, and so this defensive power of the organism is in abeyance. One of Wright's discoveries was this fact, and a second was a technic by which we are enabled to measure the quantity of opsonins in a given blood. The result of such measurement is expressed as the opsonic index. If, therefore, we say that a patient, the subject of tuberculous glands, has an opsonic index of 0.5 to the tubercle bacillus, we simply mean that his blood contains but one-half the normal

* From the Department of Immunization and Medical Research of the Toronto General Hospital.

quantity of those opsonins which are essential to combating the infection of the tubercle bacillus.

Such an observation is of great scientific interest, but as practical physicians we want to know its application to the treatment and diagnosis of disease. The question, therefore, is, given a low opsonic index in the course of a chronic bacterial infection, how can we raise that index and relieve or cure our patient? Wright provided the solution of this problem and gave us bacterial vaccines.

By a bacterial vaccine is meant "bacteria or their products." In actual practice we use bacteria grown in culture-tubes and then devitalized. The principle involved in therapeutic inoculation is that a vaccine, consisting of devitalized bacteria of the same strain as that responsible for the patient's infection, should be administered by subcutaneous injection in correct doses at appropriate times. It is in this connection that the measurement of the opsonic power of the blood aids us, and, without elaborating the argument, permit me to state as my belief that the study of the opsonic power of a patient's blood does enable us to judge the proper dose of a vaccine and the appropriate time for inoculation and reinoculation.

The principle of bacterial vaccination may be brought home to our minds by an example or two. If we have to treat a patient with boils due to infection by the *Staphylococcus pyogenes,* we will grow the staphylococcus, kill it and inoculate our patient with a proper dose of this dead culture. If our patient has tuberculous glands, we will inoculate him with new tuberculin (Bacilli emulsion), which consists of devitalized tubercle bacilli. The principle holds similarly for all bacteria that we can grow.

With this very brief summary of the basic principles, I propose to deal with a few of the results already achieved with these newly forged instruments of therapy. But first let me refer to a practical, though

tentative, classification of bacterial disease that four years' investigation of the opsonic index in many hundreds of cases has elicited.

CLASSIFICATION.

CLASS 1.—This comprises mostly chronic infections in which it has been determined that a low opsonic index is persistent. The lowered opsonic index is thought to be due to the absence of "autoinoculation" (Fig. 1). By autoinoculation is meant the escape of bacteria or their products from the focus of disease into adjacent lymph or blood streams. The result of such an escape is to increase the opsonins and other bacteriotropic substances in the blood by stimulation of the machinery of immunization and often to cure or relieve the infective process. The absence, therefore, of autoinoculation determines the persistence of the infection and indicates the necessity of interference with bacterial vaccines by means of inoculation. In this great class where autoinoculation is slight or absent there are included many tuberculous affections, such as tuberculous disease of glands, bones and early, or moderately early, pulmonary tuberculosis. We find here also boils, acne, sycosis, felons and many cases of sepsis and persistent sinuses, etc.

CLASS 2.—In this class are those cases in which autoinoculation is the characteristic feature. The more severe cases of pulmonary tuberculosis may be taken as the type. The outstanding feature of these cases is the fluctuation of the opsonic power of the blood from low to high and high to low.

CLASS 3.—This class comprises the pure septicemias. It is probable (though not yet proved) that certain of these have a generally lowered opsonic power for reasons that need not be discussed. Here are included ulcerative endocarditis, puerperal septicemia, etc.

It is in the first great class, however, where the infection is localized and where in consequence autoinocula-

tion is withheld that inoculation with bacterial vaccines has been most successful. I propose to summarize briefly the results that have been obtained, but especially to refer to cases that have come within my own experience; let me, however, first present the immunizator's method of approach by citing a particular case.

History.—The patient was a young man, aged 20, who seven weeks previously had had an empyema evacuated by resection of a rib. The daily discharge had slowly lessened to about half an ounce of pus, which gave a pure culture of the pneumococcus of Fränkel. With this bacterium as the basis of my further investigation, I determined his opsonic index and found

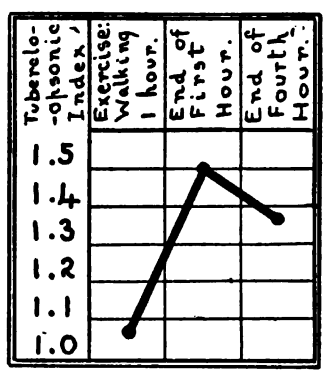

Fig. 1.—Chart illustrating "auto-inoculation" in a case of moderately severe pulmonary tuberculosis as a result of an hour's walk. The tracing shows the variation of the tuberculo-opsonic index.

it normal. Nevertheless, I thought that I might expedite matters if I raised this index and so I prepared him a vaccine by growing the pneumococcus in culture tubes, collecting the growth in salt solution and killing it at 60 C. (140 F.). Of this vaccine, I inoculated 100 millions of pneumococci with the result that his opsonic index rose quickly to 2.5. Further inoculations raised his index when it fell and by this means he was made to lead a life of increased resistance to the pneumococcus and was thus enabled to overcome his infection (Fig. 2). The clinical result was striking. In less than two weeks the discharge entirely ceased and a sinus, which though narrow had been six inches long, completely closed. The boy returned to his work and had no further trouble.

I mention this case in illustration of the principles of the method, and as a rule, therefore, we must de-

termine the particular micro-organism responsible, estimate the resistance of the patient to it, prepare a vaccine from it and inoculate in proper doses and at appropriate times as indicated by a study of the variation of his opsonic power. Time will not permit me to enter into this aspect of the subject.

Let us now consider certain groups of infections, and, since the basis of our method is bacteriologic, perhaps it

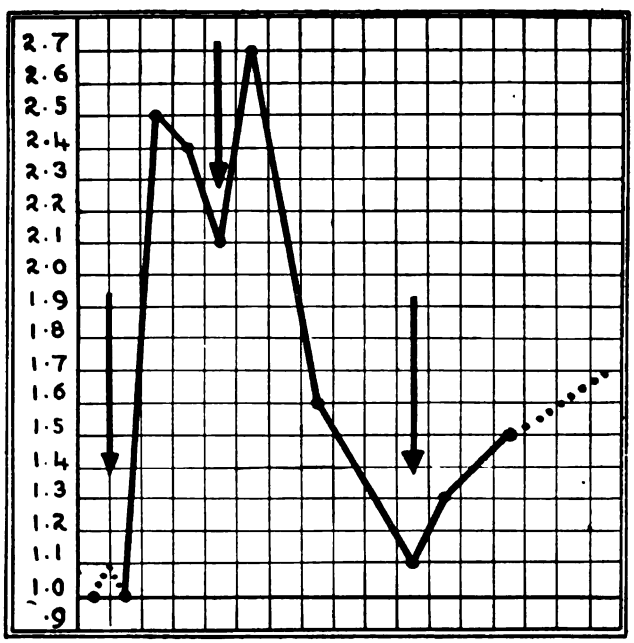

Fig. 2.—Chart referring to a case of chronic empyema sinus due to the pneumococcus of Fränkel which recovered in two weeks as a result of inoculations with 50 to 100 millions of pneumococci. The tracing shows the variation of the pneumococco-opsonic index. The arrows refer to inoculations with the homologous vaccine.

would be most direct if we viewed the subject from that standpoint. I will first discuss infections due to the *Staphylococcus pyogenes*. They are numerous and common. Some are boils, carbuncles, acne, sycosis, felons, styes and septic wounds.

The tracing shown in Figure 3 has reference to a patient who had a large and very painful furuncle on the

buttock. His opsonic index to the *Staphylococcus pyogenes aureus* before inoculation was 0.46. I then gave him 300 millions of staphylococci. His index rose to 1.5, as you see, and remained well above normal for some days. The clinical alteration in his symptoms was marked, and in 24 hours all pain and tenderness had left him. Further progress was uneventful.

I have treated eleven patients with boils—most of the cases of a very chronic or severe nature. Of those nine did well—that is to say, within forty-eight hours in most cases the pain had disappeared and also almost all tenderness. As a rule these cases proceeded to com-

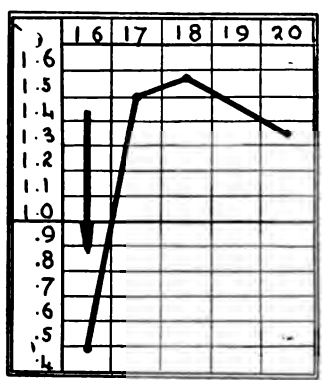

Fig. 3.—Chart illustrating the rise of the staphylococco-opsonic index as a result of one inoculation (shown by the arrow) of 300 million staphylococci in a case of furunculosis. Recovery.

plete relief without incident. Unfortunately, immunity from relapse is not assured. Some remain well for long periods, while others have a return after varying intervals. This much can be said, however, that relapses are usually of a less severe nature and, furthermore, can be easily controlled by inoculation if the treatment of the primary lesion or lesions was successful. The two patients of these eleven that were not cured improved considerably, but showed a persistent tendency to relapse. On the whole, however, I feel confident that the vast majority of cases of acute or chronic furuncu-

losis can be completely and rapidly controlled by inoculation with a staphylococcus vaccine.

In Boston I treated a patient with severe carbuncle by inoculation with a staphylococcus vaccine with striking effect. The patient was a laborer of 45 who had a carbuncle on his back as large as a baby's fist. Inoculation with 300,000,000 staphylococci removed all pain and tenderness in forty-eight hours, the central slough came away in eight days and almost all the inflammatory mass was dissipated a week later.

Altogether I have succeeded in curing or greatly benefiting the patients in five cases of acne vulgaris; still the results are considerably less striking than those obtained with furunculosis. There is a number of cases in which we completely fail—why, I do not know.

Sycosis barbæ is usually easily cured by inoculation with a staphylococcus vaccine. I have under treatment a patient with a very severe case of four years' standing. He is now almost well. Wright has reported many successful cases.

If my time was less limited I would give in detail a case of severe septic hand with scattered furuncles and also a case of orbital infection due to staphylococcus. In both the patients responded rapidly and satisfactorily to inoculation with staphylococcus vaccine.

Interesting and important as the results have been with such septic processes as I have mentioned, they hold our attention much less than those which have been obtained by inoculation with new tuberculin in many manifestations of tuberculosis. I shall now refer to several cases.

The first and one of the most striking that I know of was a case of tuberculous iritis. The patient was a boy of 12, who was sent to me by Mr. Lang of Moorfield's Eye Hospital in London. Tubercles were plainly evident on both irises and of such a severe nature on one that excision of the eye was contemplated. In addition a keratitis punctata obscured his vision. His

opsonic index was 0.85 before inoculation. I then inoculated him with 1/750 milligram of new tuberculin (bacilli emulsion), and subsequent estimations demonstrated that this inoculation had increased his index to 1.4 and higher. The inoculations were continued for about six months, when I left him in charge of Dr. Clive Reviere for further treatment. At the end of the six months all the tuberculous masses were much reduced in size and one had practically disappeared. The keratitis had almost completely cleared up. This case, in which one could actually see the tuberculous masses melt away under specific treatment, seems to me to be evidence of the benefit resulting from the use of tuberculin in localized tuberculosis.

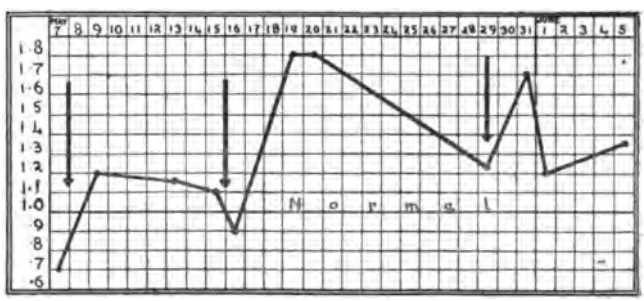

Fig. 4.—Chart referring to a case of tuberculous cystitis showing the variation of the tuberculo-opsonic index as a result of inoculations with tuberculin. The arrows refer to inoculations of 1/750 m.g. of tuberculin. Recovery.

I show also the chart (Fig. 4) of a young man aged 22, the subject of a tuberculous cystitis. Tubercle bacilli were easily found in his urine and cystoscopic examination revealed a tuberculous ulcer on the trigone of the bladder. He had frequency of micturition and continued perineal pain. There was little clinical evidence of improvement for three or four months, during which time his opsonic power was maintained at a comparatively high level by repeated inoculations with tuberculin. Then within a week or two the frequency and pain left him and he soon returned to a normal healthy condition. The tubercle bacilli also disappeared

from his urine. Nine months later a condition of excellent health obtained and he expressed himself as quite well.

I have treated only two patients with tuberculous glands and both of these did remarkably well. Indeed, it would seem that treatment of this condition by tuberculin constitutes a real triumph for inoculation. Sir Almroth Wright has treated many patients, and when I last saw him he had yet to meet with a failure. Time will not permit me to detail these cases.

I have successfully treated one patient with lupus. Lupus, however, has proved refractory to tuberculin and on the whole we fail in this condition as often as we succeed. On the contrary, tuberculous dermatitis usually responds most satisfactorily to inoculation. I have seen the patients in several cases that might reasonably have been termed desperate respond in a truly wonderful fashion to inoculation with tuberculin. I know also of cases of tuberculous kidney, of tuberculous epididymitis and orchitis, of tuberculous disease of bones and joints and of tuberculous peritonitis in which, to all intents and purposes, the patients have been cured by inoculation with tuberculin, but I can not stop to consider these cases.

The subject of pulmonary tuberculosis would be in itself a more than sufficient theme for an address, but time will only permit me to summarize. I have treated the patients in some fourteen such cases with tuberculin. Less than half were moderately early, the rest were severe. I can only state my belief on this matter, and it is that unless the case be early or moderately early inoculation with tuberculin will be of little or no benefit. As concerns the early cases, however, I hold a contrary opinion, and my belief is that tuberculin is a powerful expedient for good if rightly used. It would be absurd for me to base this opinion on the few cases that I have treated, but Lawson and Stuart, Harris and others have reported a successful issue in a number of

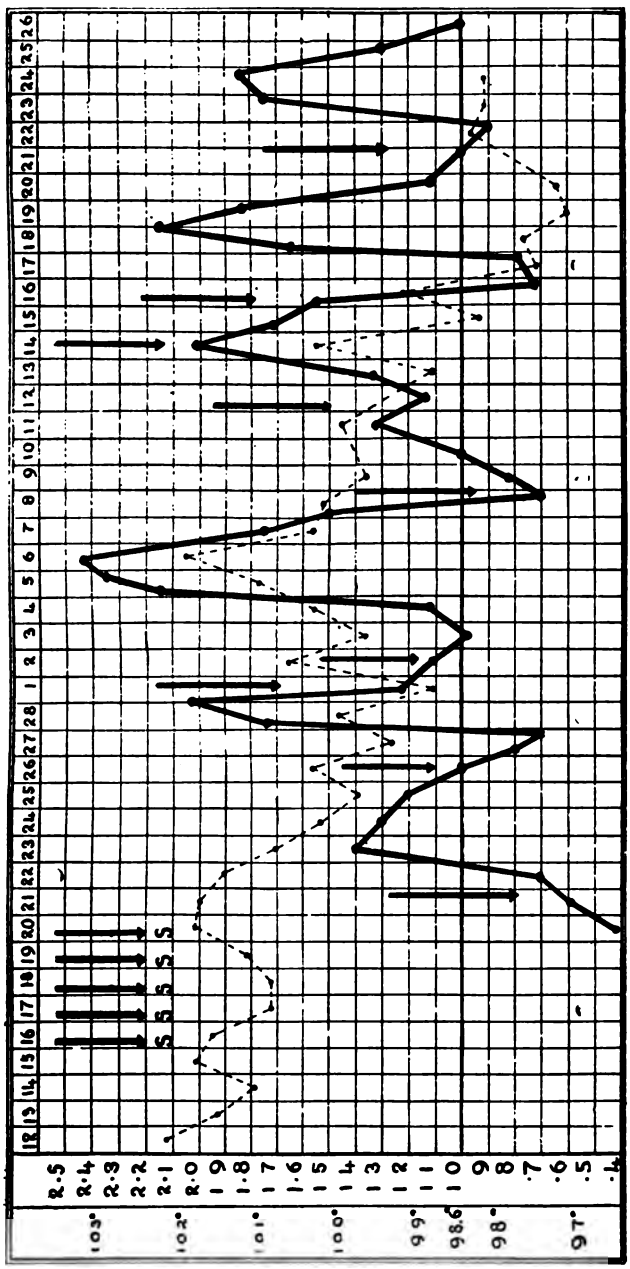

Fig. 5.—Chart (in part) of a case of malignant endocarditis due to streptococcus. The broken line refers to the temperature. The continuous line refers to the streptococco-opsonic index. "S" refers to an inoculation with an anti-streptococcus serum. The arrows refer to inoculations with an homologous streptococcus vaccine. Recovery. (Curve by Captain S. M. Douglas.)

cases. Of especial importance, however, are the results of Trudeau and his co-workers at Saranac Lake. After an experience extending over at least twelve years he is more confirmed than ever in his belief that tuberculin is a valuable remedial agent at least in the early or moderately early cases of pulmonary tuberculosis. Möller, at the Belzig Sanatorium in Germany, is also an enthusiastic advocate of tuberculin in pulmonary tuberculosis.

The streptococcus in one or another of its strains is responsible for many chronic or subacute infections. I have a case of chronic sinus, following on a laparatomy, in which the patient is doing well under streptococcus vaccine. I also had a case of chronic pyemia in which the condition subsided when the patient was inoculated with streptococcus vaccine made from her own micro-organisms. Patients with chronic osteomyelitis and subacute puerperal infections also have been successfully vaccinated. Gonorrheal arthritis in quite a number of instances has responded to a gonococcus vaccine.

Patients with pneumococcus cystitis, empyemata sinuses, etc., have been successfully treated. Cases of cystitis, sinuses, etc., due to bacillus coli have responded to a colon vaccine.

Many other affections due to a number of other micro-organisms have been treated with success, but I can not stop to consider them. I shall also have to pass over that whole second class of infections to which I referred, where auto-inoculation is the characteristic, and consider for a moment a representative case of the third great class in which are included the septicemias, viz., a case of ulcerative endocarditis.

History.—The patient was a girl under the care of Sir James Barr in Liverpool. You will observe from the chart (Fig. 5) that she had considerable pyrexia extending over five weeks, before inoculation was undertaken with a vaccine prepared from a streptococcus obtained from her blood. She had had

16 injections of antistreptococcus serum with no good effect. Without going into details it is interesting to note that with the general rise of opsonic power following on inoculations with the streptococcus vaccine there occured a general lowering of her temperature until normal was reached. The clinical result was very happy, for the patient made an almost uninterrupted recovery.

Before concluding this very cursory consideration of a large subject I wish to express certain opinions concerning it—opinions founded on over two years of practical experience in the treatment of a considerable number of affections due to a variety of micro-organisms. I may state that I have endeavored to analyze all my results coldly and critically, with a due allowance for coincidence and the intervention of other, though unknown, agencies. Nevertheless I find my belief firmly established that proper inoculation with appropriate bacterial vaccines is a powerful expedient for the cure or control of many diseases due to micro-organisms. To my own mind the evidence in favor of this belief is almost overwhelming. Concerning the relation of the opsonic theory to inoculation, however, there is considerable difference of opinion. I can not discuss this question now, but my opinion is that though estimation of the opsonic index is often unnecessary, still such investigation has been and still is of great service in enabling us to determine the dosage of a particular vaccine and the appropriate time for inoculation and reinoculation when we are in doubt. That the method of estimating the opsonic index is mathematically accurate few would have the temerity to claim, but that it is sufficiently so to serve as a useful guide in the practical application of vaccine therapy to the treatment of disease few *therapeutists* who have used the methods over a sufficient length of time to justify an opinion will deny. As a practical physician, however, I am concerned with the cure or control of bacterial disease, and I am chiefly interested in opsonic methods of investigation because I believe that they do assist me in obtain-

ing a successful issue in certain difficult cases where in default of these methods I could use bacterial vaccines neither safely nor intelligently.

DISCUSSION.

DR. JOHN C. HOLLISTER, Chicago, speaking of the irregularity of the normal opsonic index, gave the results of some investigations he had made during the past eight months. The blood from eight normal individuals was taken, at irregular intervals, some times every day, or every other day, with lapses of one, two or three weeks. The results were as follows: Individual 1.—The tuberculo-opsonic index was taken 71 times. Without exception the average of any three consecutive indices lay between 0.9 and 1.1. Individual 2.—The tuberculo-opsonic index was taken 95 times. With one exception the average in any three consecutive indices lay between 0.9 and 1.1. The one exception was 0.8. Individual 3.—The tuberculo-opsonic index was taken 82 times. Without exception the average of any three consecutive indices lay between 0.9 and 1.1. Individual 4.—The tuberculo-opsonic index was taken 51 times. Without exception the average in any three consecutive indices lay between 0.9 and 1.1. Individual 5.—The tuberculo-opsonic index was taken 50 times. Without exception the average of any three consecutive indices lay between 0.9 and 1.1. The average of the averages in these five individuals, covering 71, 95, 82, 51 and 50 examinations, respectively, was 1. Again, the blood from 100 normal individuals was examined and the indices ran, with six exceptions, between 0.8 and 1.2. In two of these exceptions there was found to be a distinct family history of tuberculosis, and also clinical "suspicions" of lowered vitality. Dr. Hollister concluded that if the technic is carried out according to Wright's method, and by capable investigators, or if the technic is carried out by two or more capable persons, the same results will obtain in at least 95 per cent. of cases. Finally, these results will bring the normal opsonic index in tuberculosis between 0.8 and 1.2. If it is found that the opsonic index in three consecutive examinations is below 0.8 or above 1.2, that person's serum is abnormal.

DR. WILLARD H. HUTCHINGS, Detroit, agreed with Dr. Ross that the question seems to divide itself into two parts: First, the therapeutic value of bacterial vaccines, and, second, the question of the relative value of the opsonic index as a method of controlling inoculation. During the past year he has employed bacterial vaccines in a considerable number of cases, controlling their administration by careful estimation of the opsonic index as described by Wright. In his opinion the therapeutic value of bacterial vaccines has been demonstrated conclusively, and the great question at present is that of dos-

age, the size and frequency of administration of which seems to vary greatly with different individuals. Concerning the value of the opsonic index as a method of controlling this dosage, he is at present undecided. In some cases he has found it of the utmost value and in others it has not served as an accurate guide. However, as Dr. Ross stated, it is the best thing we have at present and while it must be modified before coming into general use, Dr. Hutchings does not believe that we are justified, at present, in basing the treatment of cases by this method on clinical symptoms. This is particularly true of tuberculosis, where he has found the identical dose produce, at one time, a prompt rise of the patient's resistance, and at another a prolonged negative phase. He has found the negative phase extremely variable, so much so that had he inoculated at regular intervals he would have inoculated during a negative phase. Dr. Hutchings believes that 1/1000 mg. T. R. is too large a dose to begin with, particularly in children, for while it causes a decided rise in the index, later the opsonic producing power seems to be exhausted, and following repeated doses there is no improvement. He begins with 1/4000 mg. or 1/3000 mg., and rarely goes above 1/2000 mg. These doses will practically give rise in the index and the same clinical improvement. The question of the practical value of the bacterial vaccines seems to be clearly proved. In a large majority of the cases Dr. Hutchings found that the autogenous vaccines do better in the treatment of surgical conditions than anything we have had before. But one must not use bacterial vaccines to the exclusion of other methods of treatment. He recalled one case of tubercular tenosynovitis of both wrists which was treated for two months by inoculations of T. R., controlled by the opsonic index, with but little improvement. He then tried Bier's hyperemia with this, and the improvement was rapid and marked.

Dr. George W. Ross, Toronto, Canada, said that he fears greatly that the opsonic theory and vaccine therapy will suffer more from over-exploitation than from conservatism in their application to the treatment of disease. What is most desired, he said, is conservatism, and particularly the use of Sir Almoth Wright's methods by capable men, properly trained for the work. Splendid results in many cases not amenable to the usual methods certainly will be obtained if the treatment by vaccination is thoroughly done. He said that he looks forward to the time when training in this therapy will be provided by medical schools.

PREPARED AND PREDIGESTED FOODS.

GRAHAM LUSK.
NEW YORK CITY.

Economists tell us that in the struggle for existence a quarter of the income of a civilized family is paid out for lodging, a quarter for clothing and a half for food. The savage, who requires neither clothes nor modern lodging, expends his economic force in the capture of game and the raising of corn. In view of the physical well-being of savage races and of ignorant peoples throughout the world, it must at once be apparent that the normal instinct of appetite is a faithful guide for the nutritive requirement of mankind.

There will be no escape from the judgment, "By the sweat of thy brow shalt thou eat bread," until some one realizing the dream of Berthelot shall perfect a cheap process for the manufacture of veritable ambrosia from sawdust. Emil Fischer has been pictured in a cartoon as the master of a food factory located at a coal mine. Fischer, however, remarks that he who would eat his synthetically prepared sugars and peptones must, indeed, be a wealthy person.

Man is a machine developing mechanical energy and producing heat at the expense of the potential energy contained in fat, starch and proteid. A widespread error is that this requirement for energy is variable and may be largely reduced by diminishing the intake of food. Such a belief on the part of a healthy man is automatically corrected by his appetite, leading him to eat more bread for example. But where the individual is under the care of a physician, taking his food by the

physician's orders, the food requirement of the body should be very clearly understood.

Two points stand out boldly in this connection. In the first place there must be sufficient proteid food ingested to protect the organism from proteid loss, and secondly there must be given a sufficient heat value in fats or carbohydrates to protect the body fat of the person and prevent emaciation. As regards the proteid requirement, it has been found by many investigators that the average fasting man eliminates 10 grams of nitrogen in his urine, which corresponds to a destruction of 62.5 grams of proteid or the equivalent of about 300 grams of meat per day.

After prolonged fasting with extreme emaciation the nitrogen in the urine may sink to 5 grams or half what it was at first. In the case of starvation, proteid metabolism furnishes about 15 per cent. of the total fuel required by the organism and the remaining 85 per cent. is obtained by burning the body's fat. If carbohydrates be introduced alone into the circulation of a man who previously has been fasting the proteid metabolism is considerably reduced. It has also been found that where a mixed diet rich in carbohydrates is given containing 60, 50, or even 25 grams of proteid, a loss of body proteid may be prevented. In other words, the nitrogen contained in the proteid ingested is exactly eliminated in the excreta without any draft on the body's own proteid store. Such a condition is known as nitrogen equilibrium.

I do not wish to be misunderstood as commending these possible minima of proteid ingestion as being the most desirable, but I am citing the work of Chittenden and others only to emphasize the minimum of proteid ingestion below which waste of body proteid ensues. I agree with Meltzer in the idea that such a minimum is below the "factor of safety."

Passing now to the second consideration, the fuel requirement of the organism, it has been found repeatedly

that a fasting man at light work and weighing 70 kilograms produces 2,240 calories of heat or 32 calories per kilogram in twenty-four hours. This is the fasting man's requirement of energy. It may be otherwise stated as being that quantity of heat capable of raising 22.4 liters of ice cold water to the boiling point. If this person were fed on a mixed diet his requirement of energy would be raised from 32 to 35 calories per kilogram of body weight. It is, therefore, apparent that food only slightly increases heat production. If too much food be given it is retained in the body; if too little, the body substance is attacked to make up the requirement of energy. It must, however, be remembered by the physician that in the case of persons confined to their beds this requirement falls to 1,750 calories, or 25 calories per kilogram, since equable temperature and muscular rest reduce the amount of needed fuel.

Ignorance of the unremitting demands of the organism for a definite quantity of dynamic energy leads to great error. I have in mind a diabetic woman whose physician told her to take a "proteid diet" without telling her to take 200 grams of fat as well, and who as a result lost 105 pounds in three months.

As concrete examples of a ration covering the energy requirement of the normal organism it may be said that two pound loaves of bread contain 2,390 calories and 64.4 grams of proteid substances, while four quarts of milk yield about 2,400 calories and contain 140 grams of proteid. The bread costs 10, the milk 20 cents. It is evident that this quantity of fuel for the human machine is not to be compressed into insignificant pellets. The ration of dried meat called pemmican, and of half a pound and more of fat, represents the most concentrated arrangement of fuel value and is used by travelers in polar regions.

The mention of bread, or of milk, or of bread and milk, as a constant dietary arouses at once the feeling

of personal distaste. Bread and milk are easily digestible and perfectly assimilable by any healthy person, but foods with a stronger flavor are usually sought for the maintenance of the body functions. Herein lies a harvest for the proprietors of any pleasant tasting substance which is sufficiently advertised. Among such substances are the "breakfast foods."

Take, for example, "grape-nuts"—a malted preparation of the entire wheat grain—which contains a large amount of soluble carbohydrate. A pound and a half of "grape-nuts" yields 2,580 calories, contains 81.5 grams of proteid and proteid-like substances, and costs 21 cents. Here then is a product, a pound of which has nearly one and one-half times the nutritive value of a pound of bread and which costs only twice as much as bread for use in nutrition. The extra price is a price for flavor alone. The advertised statement that the system will absorb a greater amount of nourishment from a pound of grape-nuts than from ten pounds of bread is obviously a falsehood, and for any one to believe that grape-nuts is in any way more specifically adapted as a food for brain and nerve centers than is, for example, bread and milk, is preposterously foolish. Grape-nuts has been selected because it is at present the most widely advertised of the breakfast foods, but the same analysis holds true of all. For many years the name of Voit was used as guaranteeing the purity of "Liebig's meat extract," yet all Voit's publications showed that the whole value of this material was in its flavor.

As regards the fuel value of the various malt extracts one may copy the statement of Hutchison in his "Food and Dietetics" that a dessertspoonful has a fuel value of 60 calories, or less than the same measure of honey, which contains 75 calories. The sugar of honey is invert sugar and ready for immediate assimilation.

There are numerous fabrications in the form of biscuit or crackers, and these are often fortified by the ad-

dition of casein or gluten. In so far as these are pleasing to the taste they are helpful to the digestion. The question of their food value concerns the physician only in the case of diabetic patients. Such patients covet carbohydrates, and biscuit may be prepared containing 80 per cent. of gluten and only 10 per cent. of starch which may greatly comfort the sufferer. Diabetic foods have been analyzed recently by Winton of the Connecticut Agricultural Experiment Station, who shows that some of the widely used "diabetic flours" are scarcely different from ordinary flour and constitute base and contemptible frauds.

The value of cod liver oil lies not entirely in the fat which it contains, but in the presence of a large quantity of fatty acid. When the latter reaches the intestine it forms a soap with the alkali, and this soap produces an emulsion of any fat which may be present, thereby giving an immediate opportunity for the action of the digestive ferment steapsin.

All of the peptone preparations consist chiefly of albumoses. Voit has pointed out that these substances are likely to produce diarrhea, and Cohnheim states that it is undesirable to administer more than 30 grams of somatose daily to a man. Such a quantity contains about 18 grams of proteid matter.

Finally there is a class of predigested proteids which are sold in solution and are commended to the purchaser in doses of one-half to one tablespoonful. Characteristic of this group are liquid peptonoids and panopepton, of similar composition and both containing considerable alcohol. As regards these preparations, the physician must remember that a tablespoonful contains only a gram of proteid material. Also that a whole pint bottle contains about 25 grams of proteid and as much alcohol as in a quart bottle of claret. Assuming that the proteids contained in these preparations are of a physiologically valuable type, then at least a pint a day would be absolutely essential to prevent loss of body proteid. It is

said that many patients have died of proteid starvation through the ill-advised administration of these preparations. It may well be that these liquid foods are sometimes helpful as flavor and stimulant, but their limitations should be fully recognized.

It seems that the physician should be rightly informed as regards the requirements of nutrition. It would be well to remember the ready digestibility of white of egg, of beef juice, of peptonized milk. The wonderful improvement in the nourishment of hand-fed children should stimulate to further research along this line. No doubt much help will come from the dilution and subsequent enrichment of milk with cream and milk-sugar and the study of its action on the organism in disease. The basis of nutrition, whether in childhood or in the adult, in sickness or in convalescence, requires the administration of the proper quantity of proteid and of energy containing fats and carbohydrates and the preparation of this food in a palatable form.

DISCUSSION.

DR. S. J. MELTZER, New York, said that he hoped the members of the Section would know that Dr. Lusk is one of our best authorities on the questions pertaining to metabolism, and that his coming out firmly against many of these foods is to be regarded as a brave, public-spirited act.

DR. W. S. THAYER, Baltimore, said that he considered Dr. Lusk's book on the "Science of Nutrition" one of the most valuable works on the subject for the general practitioner; indeed, he felt that it was the most important addition to his library during the past year.

DR. W. A. WITHERSPOON, Nashville, Tenn., said that for a long time many have depended on these so-called predigested foods. It is simply marvelous what amounts are sold. Persons throughout the country have an idea that because the stomach will not reject some of the foods mentioned by Dr. Lusk that they are ideal foods. This is an error, for the majority of them have no nutriment and are prepared entirely for commercial purposes. He felt that Dr. Lusk would confer on the Section a great benefit if he would demonstrate, and let it be known, what these foods really consist of; let it be well known that the Section stamps its disapproval on these products. In treating the convalescent and the patient with gastro-

intestinal disorders, the physician should take into consideration that they do better if given more beef juice, eggs, albumin, true foods, and that they should depend less on what is made with little science and offered for commercial purposes.

DR. WOODS HUTCHINSON, New York, said that physicians' responsibility to the public should be considered. After referring to what Smith and Adams have done in their crusade against quack remedies, he said that the gun should be turned against some of the medical journals whose pages are filled with their advertisements. Not only is there a low proteid content in these predigested foods, but a considerable part of the proteid is so changed in the process of preparation that it is no longer valuable in the animal economy.

A CRITICAL ESTIMATE OF THE FERMENTATION SPECIFIC GRAVITY METHOD OF QUANTITATING SUGAR IN DIABETIC URINE.

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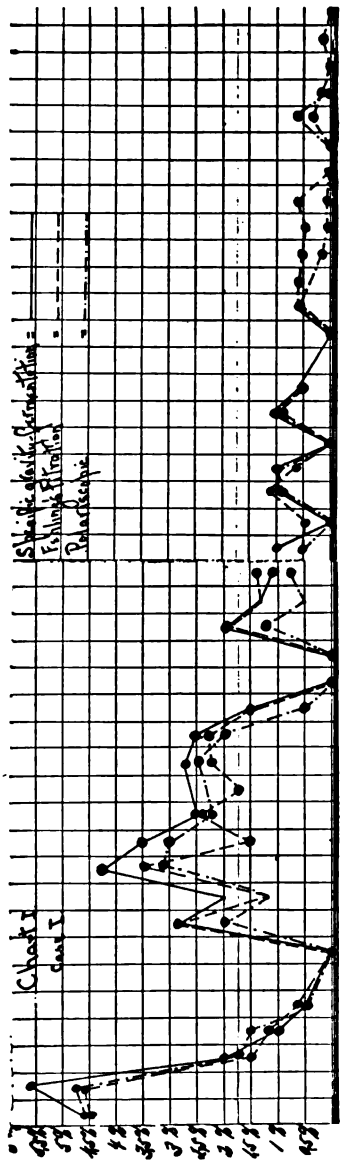
In 1861 Roberts[1] described a method of quantitating the glucose present in diabetic urine, which he spoke of as "the clinical method," on account of its simplicity and ease of application. His method consisted in determining the decrease in specific gravity of the urine caused by the action of yeast. Yeast fermentation splits up the glucose present, and its amount can be determined by multiplying the difference between the specific gravity of the urine before and after fermentation by 0.23. This gives the percentage of glucose present. Roberts compared the results obtained by this with those from other methods of that day for quantitating glucose, and showed the considerable accuracy of his method.

Of late years the method suggested by Roberts has been rather neglected. In its place titration with some form of copper sulphate solution, polariscopic estimation, a fermentation method which measures the amount of carbon dioxid formed in the destruction of glucose, or other methods have been very generally used and comparison of the results of these various methods have been published by a number of observers.

1. Edinburgh Med. Jour., 1861, vii, 326.



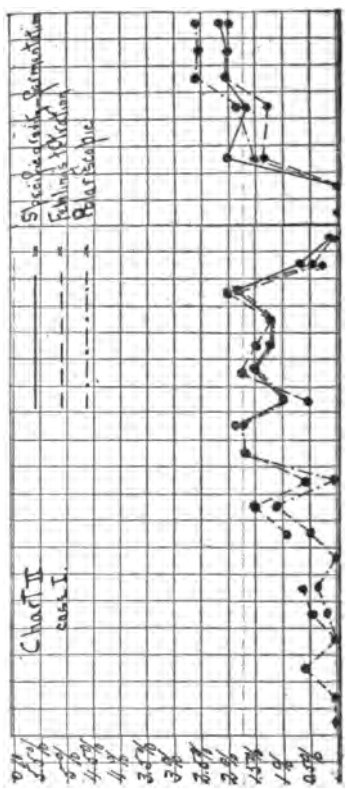


CHART I, CASE I. Results of estimating the sugar in diabetic urine by the three methods.

CHART II, CASE I (continued).

Of all methods the fermentation-specific gravity one appears to be the simplest for the general practitioner, because it requires no laboratory and needs only a bit of yeast from the kitchen and the urinometer or specific gravity bulb, which every physician has. How accurate is such a simple method?

The question of accuracy is to be answered by comparing the results of this method with those obtained with other methods. During the past two years I have been able, with the aid of picked students from the fourth-year class of the Harvard Medical School, working under my direction at the Massachusetts General Hospital, to make such a comparison. We have made daily quantitations of the sugar present in the urine of several diabetic patients by (1) the Fehling's copper sulphate titration method; (2) the polariscopic method; and (3) the fermentation-specific gravity method. The estimates have been made in part by myself, largely by the students under my supervision. It has been our attempt to apply each method with such care and attention to detail as might be expected of a careful clinician working with adequate laboratory facilities. As a matter of fact, on the whole, more estimates of a given specimen were made and more attention was given to the avoidance of some of the commoner sources of error than it is fair to expect of even a very careful clinician. The polariscopic estimations were made with a Schmidt and Hensch half-shadow saccharometer, and these results were controlled by a more accurate polariscope from the same makers.

The results of these estimations are graphically shown in Charts I to VIII. A glance at these shows a close agreement in the various quantitations. Chart III, which differs somewhat from the others, is from a case in which during the first few days there appeared to be excretion of both levulose and glucose. At least this supposition would satisfactorily explain the considerable difference between the results of polariscopic estimation

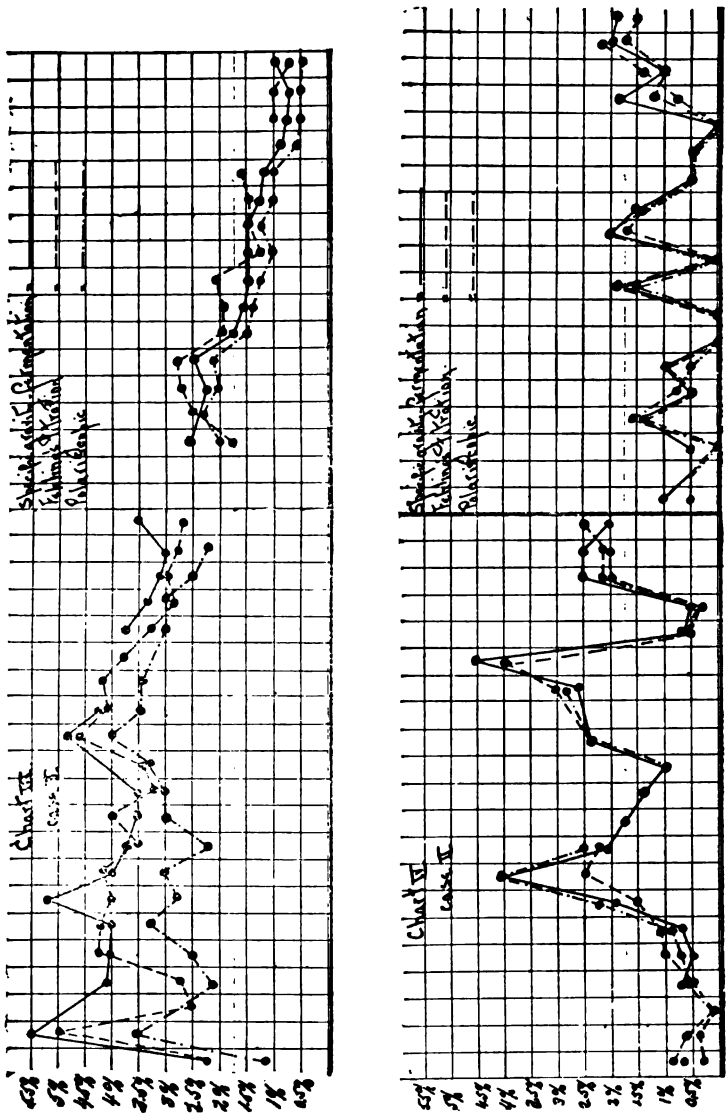


CHART III, CASE II. Results of estimating the sugar in diabetic urine by the three methods.

CHART IV, CASE II (continued).

and those from the other methods. At the same time the urine on these days gave a strongly positive reaction with Seliwanoff's reagent, which reaction later disappeared. The occasional sudden variations seen in the other curves are probably due to errors in application of the method. All were typical cases of diabetes mellitus of moderate severity. In none was there coma or evidence of impending coma. The quantitations represent the per cent. of glucose in a mixed specimen from the total twenty-four-hour amount.

Chart IX shows the results of quantitating (*a*) normal urine to which glucose (Kahlbaum c. p.) has been added, and (*b*) 1 per cent. sodium chlorid solution, in

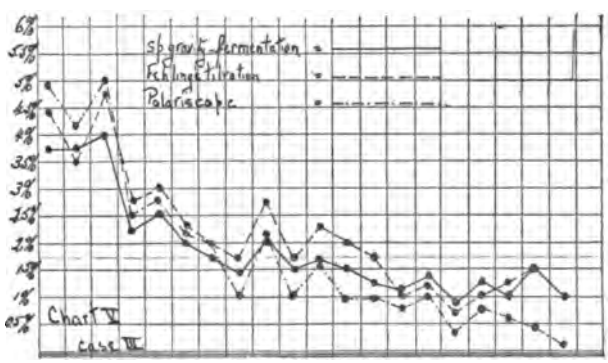


CHART V, CASE III. Results of estimating the sugar in diabetic urine by the three methods.

which glucose similarly was present. This shows a close analogy to the results obtained in diabetic urines.

To titrate a diabetic urine with Fehling's solution requires a considerable amount of time, care and laboratory equipment. The end reaction is not very sharp, and there is a considerable inherent error in the method. The polariscopic method requires an expensive instrument and the accuracy of the result is influenced by the presence of beta-oxybutyric acid, albumin, levulose and other possible constituents of diabetic urine.

The fermentation-specific gravity method as shown by the charts gives results as good as do the other methods.

It is very simple in application, requires no laboratory equipment and involves a minimal cost for apparatus. All that is required is to take the specific gravity of the urine at room temperature, add a small bit of commercial yeast and place in a warm place, such as an incubator at 37 C., a heated room, near a stove or radiator, etc. Active fermentation soon begins and is evinced by bubbles and currents in the urine. When fermentation is finished the specimen partially clears and the evolution of gas ceases. A negative test with Fehling's or Nylander's solution proves the end of the process—twelve to eighteen hours is usually sufficient. The specimen is now allowed to return to the room temperature

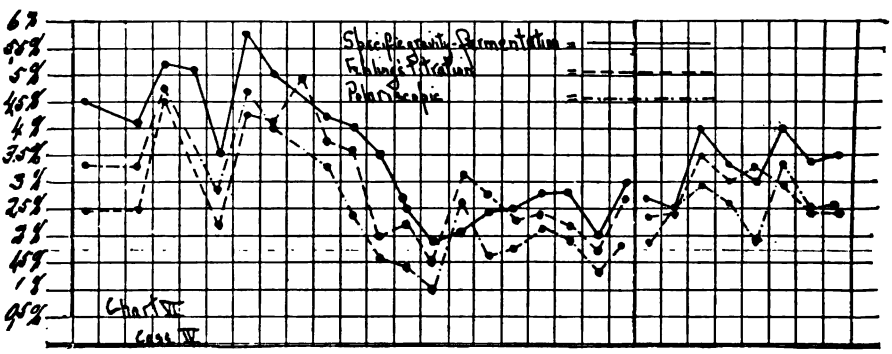
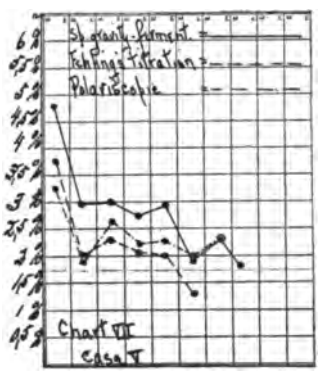


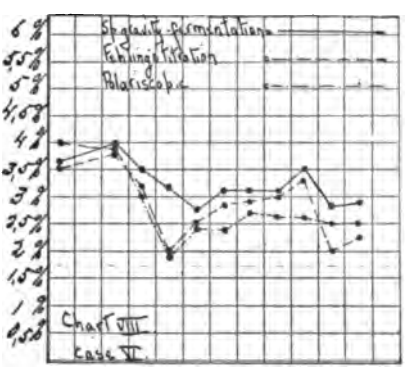
CHART VI. CASE IV. Results of estimating the sugar in diabetic urine by the three methods.

of the previous specific gravity determination, and the specific gravity redetermined. The difference between these two readings, multiplied by 0.23, gives the percentage of fermentable substance expressed in terms of glucose.

A number of specimens were carefully filtered before the second specific gravity determination was made. This made no appreciable difference. The specific gravity bulb used was such as is sold to the physicians at a cost of from fifty to seventy-five cents. Many comparative readings were made, using a more accurately graduated longer specific gravity bulb and calculating the

necessary allowance for temperature changes. Here again the differences are very slight, so slight that they might well be neglected. It is, however, important to use the same specific gravity bulb for both readings, since these cheap instruments vary considerably in their





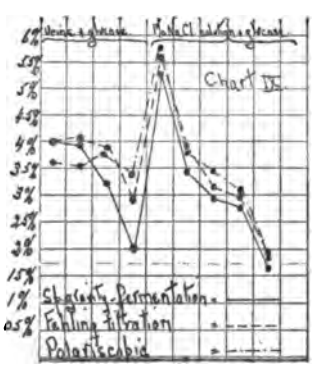


CHART VII, CASE V. Results of estimating the sugar in diabetic urine by the three methods.

CHART VIII, CASE VI. Results of estimating sugar in diabetic urine by the three methods.

CHART IX. Results of estimating glucose dissolved in normal urine and in 1% solution of sodium chlorid by the three methods.

1,000 level. Moreover, the specimen should be approximately at the same temperature at each reading, or a specimen with and without yeast be kept side by side and simultaneous specific gravity readings be made after

the completion of the fermentation in one, as first suggested by Roberts, for any considerable temperature variation will affect the specific gravity enough to change materially the result of the determination. Observing these few precautions, the results obtained are about as accurate as those given by the other two methods. The great simplicity of the fermentation-specific gravity method renders the chance of error in application slight, and it can be strongly recommended to the general practitioner in following the metabolism of cases of diabetes mellitus.

The facts presented above are not new. Yet it has seemed worth while again to call attention to so simple a method of quantitating glucose in urine, and to commend it as a sufficiently accurate method to enable the practitioner to treat scientifically his cases of diabetes mellitus. This is the motive of the paper. An accuracy sufficient for more exact chemical work is not claimed.

DISCUSSION.

DR. HEINRICH STERN, New York, said that Dr. Christian pronounces the same idea concerning Robert's fermentation test which he has stated during the last nine or ten years. Instead of multiplying the difference of degrees before and after fermentation with 0.23, more exact results will be obtained by multiplying with 0.2288. Dr. Stern expressed the opinion that the estimation of glucose by the evolved carbon dioxid is a very inexact method, and that the fermentation tubes, devised for this method, are nothing but makeshifts and playthings. Dr. Stern said that he designed the urino-glucosometer, a very accurate apparatus, about nine years ago, to facilitate the execution of Robert's method. Ordinary urinometers are rarely accurate. A good instrument can not be made for 50 or 60 cents. It will be found that they all give more or less different readings. The urino-glucosometer is composed of two tubes, one containing 50 c.c., the other 100 c.c. Both tubes are filled with urine, the yeast being added to the tube holding 100 c.c. After 12 or 18 hours, when fermentation is complete, the specific gravity is taken of the urine contained in the smaller tube. Following this, the urine in the larger tube is boiled and filtered, and its specific gravity is ascertained in the smaller tube. The number of degrees lost in fermentation is then multiplied by 0.2288, which expresses the number of grams of glucose that were contained in 100 c.c. of

the urine. The chemically-trained physician, of course, need not resort to the fermentation test. For the clinician, however, Robert's method, if executed with an accurate apparatus, is the simplest and most trustworthy test for the determination of urinary glucose.

DR. W. S. THAYER, Baltimore, said that the old fermentation test is certainly the easiest quantitative test for sugar, and, as has been demonstrated by Dr. Christian, is one of the most accurate; it has undoubtedly been considerably neglected. It is not easy for the busy practitioner to carry out other tests. Diabetes can not be properly treated unless one follows the percentage of sugar in he urine. The proper regulation of the diet, which is the essential feature in the treatment of this disease, depends largely on quantitative estimations of the excretion of sugar. This can be done anywhere by means of the fermentation test practically as well as in a hospital and with the expenditure of little time.

DR. HENRY A. CHRISTIAN, Boston, said that he found that the difference in specific gravity before and after filtration at a time when fermentation was completed was so slight that it might be neglected in estimating the results. This is wnat would be anticipated, since the solid bodies in suspension could not materially influence the specific gravity. Boiling after fermentation, in order to remove all the gas present in the urine, was tried and, of course, made some difference in the result, but boiling also drives off the alcohol produced in the fermentation, and in that way introduces a second source of error. Without boiling, the error is a small one, and for practical purposes may be neglected. Polariscopic examination after the completion of fermentation and deduction of the result of this reading from the previous reading was not done in any of the cases reported. The second polariscopic reading only corrects readings in those cases in which albumin or β-oxbutyric acid is present. The cases here studied were selected so as to include none in which albumin was present, and none of the cases showed any evidence of coma or the secretion of any considerable amount of β-oxybutyric acid.

EXPERIMENTAL ANEMIA.

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When one considers how incomplete is our knowledge of the anatomy and physiology of the hematopoietic system it is perhaps not remarkable that the diseases of that system should have remained so long shrouded in obscurity. Although the clinical pictures of the anemias and leukemias are sharply defined, their pathology still offers many problems. When in his classical description of pernicious anemia Addison noted that it occurred "without any discoverable cause," he stated the first and greatest problem of that disease and one which a half-century of investigation has not been able to solve, although by clinical, pathologic and experimental studies it has been able to narrow the field of search somewhat. However, this, the etiology of the disease, still remains its great problem.

The second problem arose at a time when the clinical picture, especially the blood picture of this anemia described by Addison, had not been sharply defined, and it arose from the description by Biermer and many others of progressive and pernicious anemias following many well-defined causes, causes almost too numerous to catalogue, and causes which in general are followed by an anemia of the so-called secondary type. This difficulty was partially cleared up by the clinicians who showed that the Addison anemia had a distinctive blood picture. It has left still unsettled, however, the question as to whether or not at some stage secondary

anemias of varied causation may not present the blood picture of pernicious anemia.

So the second problem may be stated as the relation of the primary and secondary anemias. To express it more fully, if pernicious anemia be not always due to the same cause, but to many causes, and among them to those that at times produce anemias of the secondary type, what is the factor which determines the type of blood picture?

The third problem is one that arose from the pathologic investigations of the disease. Cohnheim discovered the characteristic bone-marrow lesion of the disease, and it was later thoroughly studied by Ehrlich and others, who emphasized its greatly increased megaloblastic content as pathognomonic of the disease. As a result of these studies many have considered the bone-marrow changes as the primary lesion in the disease and accountable for the blood changes and other lesions.

Exclusive of the bone-marrow changes the pathologic study has revealed in many cases no lesions that could not be considered as secondary to the anemia, with the exception of the lesion emphasized chiefly by Quincke and Hunter. This lesion is the excessive deposition of iron-containing pigment in the liver and kidneys especially, though occurring also in the spleen and other organs. These deposits were interpreted as the result of the action of a hemolytic substance on the red blood cells and formed the basis of the theory accepted by many that the disease is essentially a hemolytic process and that hemolysis occurring in the circulation is responsible for the other lesions of the disease.

This theory received additional support from the facts that infection with the intestinal parasite, *Bothriocephalus latus*, gives the typical picture of pernicious anemia and that an extract of the worm has been shown experimentally to produce hemolysis in dogs. Yet it became evident that hemolysis alone is not adequate to explain the disease, for hemolysis with deposition of

blood pigment is a factor in secondary anemias not caused by hemorrhage.

The third problem then concerns the pathology and the pathogenesis of the disease, the value of the claims as to the primary lesion. Is there a primary bone-marrow lesion or is there an original hemolysis with subsequent changes in the marrow?

Briefly, then, the problems of pernicious anemia concern its entity as a disease and the establishment of the blood picture, its relation to other types of anemia, its pathogenesis and its etiology. All of these are not subject to experimental investigation. The establishment of the blood picture and of the disease as an entity has been done by clinicians and pathologic anatomists. A definite blood picture characteristic of the disease has been made out, and it has been determined that there is a disease corresponding to Addison's description with this definite blood picture and with pathologically a characteristic bone-marrow lesion, signs of hemolysis and no lesion otherwise, apparently adequate to explain the anemia.

For the etiology one must look to further clinical and pathologic study. On the other hand, the relation to secondary anemia, and the pathogenesis of the disease lend themselves to experimental investigation. The work of Quincke, Hunter and others in establishing the fact that hemolysis is a large factor in the production of the anemia furnished the lead along which profitable experimental work has been done. In this work the extensive study of hemolytic processes, stimulated by the Ehrlich hypothesis, has been of importance.

In the first place, it has been shown conclusively that the blood picture of pernicious anemia can be produced experimentally in such animals as the dog and the rabbit, the animals used most extensively.[1] This picture

1. The experiments forming the basis of this paper will be found in detail in the following references: Etiology and Pathogenesis of Pernicious Anemia, Johns Hopkins Hosp. Bull., 1905, xvi, 222; Experimental Anemia in the Rabbit, Jour. Exp. Med., 1906, viii, 625.

simulates the picture in human blood as closely as any pathologic picture produced in animals simulates the picture in man produced by the same etiologic agent. The blood picture in rabbits shows the nucleated red cells both megaloblastic and normoblastic, often occurring in showers. It shows further the characteristic changes in non-nucleated red cells: a variation in size, with the predominant cells above the average normal diameter; a certain amount of poikilocytosis, polychromatophilia and in many cases a granular basophilia and even an increased color index (Tallquist). Even the reduced white cell count with a relative increase of the large mononuclear variety may occur. In short, practically none of the features of the blood picture of pernicious anemia is lacking.

Furthermore, a condition of the marrow agreeing with that found in human cases may be produced—a marrow in which there is a predominance of the megaloblastic type of nucleated red cells and of cells of the large lymphocyte type. There seems to be no doubt, therefore, that one can thus produce the picture of pernicious anemia experimentally in animals.

As to the manner in which this picture can be produced it is of interest, as it bears somewhat on the possibility of a multiplicity of causes in the production of pernicious anemia in man, that it may be produced by the injection of a number of substances—but substances which have a common characteristic and that is, that they are hemolytic for the corpuscles of the experimental animal.

I have used artificially produced hemolytic sera, but chiefly ricin and saponin. Others have used pyridin, pyrogallol and other toxins. With large doses of ricin or saponin, injected intravenously and repeated at intervals, one may produce a progressive anemia with the blood picture described to the point at which the animal establishes a tolerance to the poison. The animals react with machine-like regularity to the dose of poison, with

a sharp nucleated red cell reaction and a fall in the number of red cells, with a gradual assumption by the non-nucleated red cells of the abnormalities noted.

This reaction, the blood picture and the marrow picture are entirely different from those of a secondary anemia produced in animals by hemorrhage. In these latter cases, with repeated hemorrhage and a constant fall in the red cells, there is no sharp nucleated red cell crisis; megaloblasts are not found in the circulation and normoblasts but occasionally, after the first reaction. The color-index falls rapidly, the corpuscles becoming extremely pale, and the marrow has the characteristic picture seen in cases of secondary anemia where the nucleated cells of the normoblastic type are the predominant cells. It is an entirely different picture. While this picture of pernicious anemia may be produced by several hemolytic substances it is only produced by them if they are injected into the circulation in relatively large doses, which is of importance in considering the pathogenesis of the disease.

If these hemolytic substances are injected, not intravenously but subcutaneously or intraperitoneally, the result is entirely different. The hemolysis goes on; deposits of blood pigment are found in the spleen; there is a reduction in the red cell count, but the blood picture and the marrow picture are different unless very large doses are used. The sharp nucleated red cell reaction in the circulating blood is not seen, the fall in the number of red cells is less sharp, and the marrow shows the picture of a secondary anemia with the great predominance of normoblastic cells so characteristic.

Briefly, by the injection of a large dose of hemolysin directly into the veins, one gets the primary anemia blood picture; by the injection of the same dose, or even larger doses subcutaneously, when absorption into the circulation is slow one gets the picture of a secondary anemia and a similar difference occurs in the marrow pictures.

The explanation of this difference lies, it seems to me, in the appearance of the marrow of animals dying after a recent dose of toxin. Where the toxin has been injected intravenously in sufficient doses it is not entirely saturated by red cells before it reaches the marrow and one finds as a result signs of direct injury to the marrow, in extensive necrosis of cells and in injury to the capillary endothelium resulting in minute hemorrhages. That there is hemolytic destruction of nucleated red cells is shown by naked pyknotic red cell nuclei found both in the marrow and in the circulating blood, and also larger cells in the marrow show pyknotic and fragmented nuclei. Where the injection has been subcutaneous, unless the dose of toxin has been extreme, the injury to the marrow is very slight and may even not appear.

Herein lies the explanation, I believe, of the relation of anemias of the pernicious type to those of the secondary type, due to causes other than hemorrhage. That is, in a disease like tuberculosis, in addition to the general malnutrition, there is a constant but slow absorption into the circulation of substances destructive to red blood cells. This absorption, however, is so gradual that the toxin is completely anchored by circulating red cells, causes their destruction or injury as shown by the splenic accumulation of blood pigment, but does not reach the marrow in an uncombined state. As a result the marrow escapes injury.

As far as the marrow is concerned, the lesion is the equivalent of a hemorrhage. It is uninjured and is able to repair the blood lesion in a normal way in as far as the general nutrition of the patient will permit. On the other hand, in pernicious anemia at some periods large quantities of a hemolytic poison gain entrance to the circulation, are not completely combined with circulating red cells and reach the marrow. There they cause destruction, not only of mature red cells, but of nucleated red cells and the function of the marrow is

impaired, leading to a faulty response to the call made on it to repair the lesion—and the blood picture of pernicious anemia is the result.

It seems possible in this way to explain why in certain severe secondary anemias the picture of pernicious anemia is seen in the blood. One need only postulate that in a progressing anemia there comes a time when the pathologic process, the tuberculosis for example, also progresses more rapidly, more toxin is produced to be absorbed into the circulation, there are fewer red blood cells to neutralize it, and enough of it reaches the marrow uncombined to cause an injury to the marrow cells—and then the pernicious type of blood picture results.

Why one finds this blood picture as a result of marrow injury seems to depend largely on the anatomic grouping of the cells in the marrow. As I have emphasized in previous papers, the cells seem to be so arranged in the marrow that by the multiplication of the parent cells in the erythrogenetic and leukogenetic centers the young cells as they mature are gradually pushed toward the periphery of the group and thus the mature differentiated cells, the polymorphonuclear leucocytes or the non-nucleated erythrocytes are found on the periphery close to the marrow capillaries. These mature cells are the reserve stock from which the circulating blood is supplied to fill in deficiences caused in the normal wear and tear of the circulation, and normally the marrow cells proliferate only rapidly enough to keep this supply at par.

Let there be an unusual demand, as for leucocytes in an acute inflammation, and one finds that at first the marrow is cleared of all its mature polymorphonuclear cells, and myelocytes form practically the entire white cell count in the marrow. Mitosis and maturation of the products of division, however, soon produce an abundance, usually a superabundance, of polymorphous cells, and the demand is supplied. Occasionally, as in

acute lobar pneumonia, the great demand for leucocytes may cause the marrow to react with immature white cells, myelocytes—which are often found in small percentage just before the crisis in that disease.

A similar story is that of the red cells. In a hemorrhage of moderate severity the marrow responds with its mature red cells and proliferation of nucleated cells takes place to supply the demand. Commonly the demand exceeds the supply of mature red cells and normoblasts are contributed to the circulating blood, but seldom in great numbers. Megaloblasts only extremely rarely are found in the stream.

This is the reaction in a hemorrhage or secondary anemia, and if the cause be withdrawn the blood count gradually returns to the normal as the result of this reaction of an unimpaired marrow. In man one misses a hypererythrocytosis corresponding to the leucocytosis which expresses the pathologic reaction in excess. This probably is due to the fact that serum withdrawals from the tissue keep the red cells diluted to the normal number, even though they be produced in excess. In an animal like the rabbit, with dry tissues, a reaction in excess may be obtained, with high red cell counts in the circulation, and then a gradual return to the normal.

Now in the cases with marrow injury we have an entirely different reaction, for the reason, it appears, that the toxin reaches first these mature red blood cells and the normoblasts and causes their destruction in part. In its first response the marrow throws into the circulating blood the most peripheral and most mature cells left, and these are often normoblasts and intermediates which appear in the circulation in a shower often aggregating thousands per cubic millimeter.

If the injury be more severe, intermediate nucleated red cells and even megaloblasts appear in the circulation as the other cells have been destroyed. This, however, is ruinous to the proliferative power of the marrow; cells capable of mitosis have been lost to it. As a result,

with this continued demand for red cells, there is a hasty transition from megaloblast to erythrocyte—without the orderly progression, through intermediate and normoblastic stages. The resulting cell is thus larger than normal, bears more hemoglobin and possibly is an attempt at compensation—an attempt to make quickly a cell which shall be the equivalent of more than a single normal cell. The distorted forms are expression also of this faulty hematopoiesis.

The nucleated red blood cell crises or showers so widely considered as signs of regeneration on the part of the marrow can not be so considered from the results of experimental anemias. They do not occur during recovery from hemorrhage or injury, but only immediately following direct injury to the marrow by toxins, and it would appear must be interpreted as the result of that injury. The marrow deprived of its mature red cells responds with the nearest substitute it has—the immature nucleated red cells. The greater the injury to the marrow, so much less the maturity of the cells which it can offer to supply the deficiency, so after severe or repeated injury the number of megaloblasts which are found in the circulation is increased and they are in a way an index of the gravity of the lesion.

On the evidence then of experimental work and of pathologic study it seems justifiable to conclude as to the pathogenesis of pernicious anemia that it is due to the absorption into the circulation of a substance or substances of hemolytic power toward human red blood cells, and in such quantities that it produces not only destruction of circulating red blood cells, but also destruction of, and injury to, cells of the erythrogenetic groups in the bone-marrow. This results in a defective and atypical blood formation, some phases of which may be considered as an attempt at compensation, others as a sign of injury.

One may conclude further that in secondary anemias there is a loss of red blood cells or a destruction of red

blood cells by toxins. In either case the marrow is unaffected except in being stimulated to respond in a normal manner with the orderly production of non-nucleated red blood cells, and that its proliferative power is not impaired. At some point in the disease, however, the amount of toxin may be so increased that the marrow becomes injured and the blood picture becomes of the pernicious anemia type.

As to the source and nature of this poison in pernicious anemia, there is little to add. In one type only, the *Bothriocephalus* infections, has it been determined. In those cases the source is the intestine, the poison a hemolytic substance derived from the worm. Such cases may recover, with a normal blood picture, after removal of the parasite.

In the great majority of cases no *Bothriocephalus* infection exists. In these one must assume another cause. There is a tendency, however, on the basis of clinical and pathologic findings, to regard the gastrointestinal tract as the source of intoxication. From the clinical side gastrointestinal symptoms in pernicious anemia patients are frequent and often severe, the persistent diarrhea with the general weakness furnishing the reason that brings the patient to the doctor.

From a pathologic standpoint a chronic gastritis is a frequent lesion found in the patients, and Hunter has called attention to the frequency with which oral sepsis and in particular a chronic glossitis are found in these cases. He considers that the infection of the mouth extending to lower portions of the gastrointestinal tract is the cause of the disease.

There seems to me much in this theory of Hunter's, and while I can quote no large series of personal investigations of the oral cavity, I would like to record that in two recent cases of pernicious anemia in which the oral cavity was examined there were found extensive dental caries and pyorrhea alveolaris, and also at the base of the tongue a chronic inflammatory process, in

one of the cases, with shallow superficial ulceration. In the other case there was no ulceration but a degeneration and numerical atrophy of the tongue muscle and a deep sclerosis with round cell infiltration and hyperplasia of the mucous glands.

In both cases there was also a chronic gastritis. There were no other lesions found to which the anemia might be attributed. I hesitate to lay much stress on the importance of this chronic glossitis, as I am unable to furnish control statistics as to the microscopic condition of the tongue in cases dying of other diseases than anemia. I have, however, failed to observe the glossitis grossly.

If the lesion be due to infection of the gastrointestinal tract the clinical history of partial or almost complete recovery of the patient with subsequent relapse, or repeated alternation of these states, would suggest that the infecting organism was one against which a lasting immunity was not obtained. It may be one which possibly leaves the patient even more susceptible—the common history in infections by the organisms of the streptococcus, pneumococcus and gonococcus groups. There is no absolute evidence that the organism does belong to that group, and yet there appears to be no evidence that it does not. As to etiology, we must still say with Addison as to the great number of cases, that it is a disease without any discoverable cause whatever.

UNCINARIASIS, ITS DEVELOPMENT, COURSE AND TREATMENT.

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AND

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WASHINGTON, D. C.

In this paper we purpose to confine our attention to the disease uncinariasis, inasmuch as a detailed description of the methods of the Porto Rico Anemia Commission in combating the present epidemic in Porto Rico has been made the subject of other papers written by us. Suffice it to say that, at the beginning of its operations, the commission found itself confronted by an epidemic affecting about ninety per cent of the rural population of the island, with an average of 20 per cent. to 25 per cent. of the total death rate for some years previous to the year 1905 (*Health Reports of Porto Rico;* deaths from anemia, 1898-1904, inclusive).

Our experience extends over the period 1899-1906, in the last two years of which the commission treated about 30,000 persons, fully 12,000 of whom came under our personal care and attention. Dr. Pedro Gutierrez, of Porto Rico, the other member of the commission, shared with us the difficulties of that work and took an active part in conclusions drawn from it. He is now chairman of the present commission, which has already treated, since June, 1906, about 85,000 patients.

We believe the skin route to be the only efficient mode of invasion of *Nectator americanus* in producing uncinariasis, as infections by the mouth are not only rare, but, if thus consummated, the larvæ are so few in number as to be an insignificant factor in producing symptoms. That larvæ may be introduced into the digestive canal by the mouth and become parasitic therein seems to have been proved. Ninety-six per cent. of our patients acknowledge having had "mazamorra" or ground itch, a lesion abundantly shown to be due to invasion of the healthy skin by these larvæ, and the well-shod were practically never infected, though living in the midst of this tremendous epidemic. We feel justified, therefore, in considering that the remarkable claim of Loos, Claude Smith and others, has been established on a sufficiently extensive scale as the usual mode of invasion, in Porto Rico, at least.

Contact of the skin with mud laden with encysted larvæ for a time not necessarily longer than from a few minutes to half an hour, causes first itching, then redness and swelling of the part, with the formation in a couple of days of papules, rapidly becoming vesicles. In favorable cases pustulation does not occur, but when the invasion of many larvæ has profoundly inflamed the part and the ordinary organisms of pus have gained a foothold, not only do pustules form, but extensive ulceration may result which is extremely resistant to treatment. In the case of an American officer, the severity of these ulcers caused his invaliding to a military hospital in the United States, the manner of his infection having been from mud which during a "hike" had oozed between the top of the shoe and the legging.

Extensive ulceration and the scars left by it on the lower third of the leg were very frequent among our patients. Such ulcers were those dubbed "tropical" by the uninitiated, "syphilitic" by those whose knowledge of the country people of Porto Rico was not extensive.

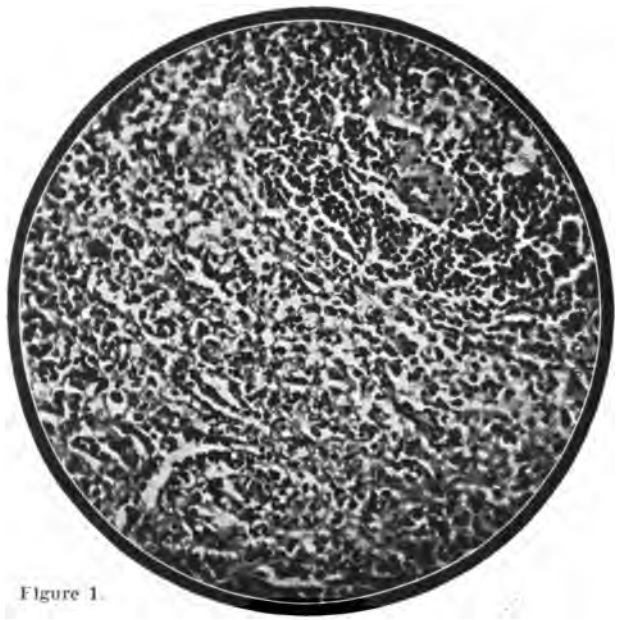

Figure 1.

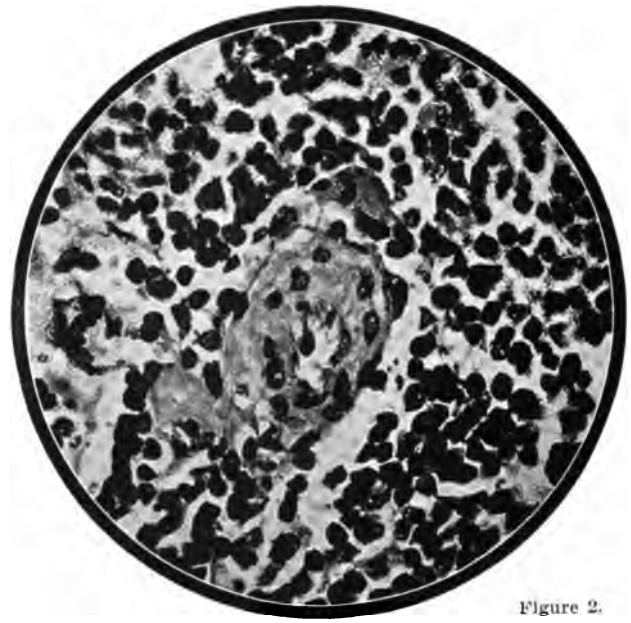

Figure 2.

Fig. 1.—Photomicrograph of spleen in uncinariasis, × 200. By Dr. W. M. Gray. All the sections from which these four illustrations were made were from the organs of two individuals dying of very extreme and uncomplicated uncinariasis, chronic type. Hb. of one case of 10 per cent. The sections are from 4 to 5 micra in thickness. The specimens were hardened in Zenker's fluid.

Fig. 2.—Photomicrograph of spleen in uncinariasis, × 500; same specimen as in Figure 1. Showing central artery, Malpighian corpuscle and hyaline degeneration. By Dr. W. M. Gray.

Generally, in milder invasions the dermatitis subsides in a week or two. We believe that skin infection can take place without manifest dermatitis, judging from a number of cases in which mouth infection seems to have been improbable. In fact, we accomplished, by the skin route, an infection of a guinea-pig which was so severe as to cause its death in three and a half days, although the outward signs of ground itch never appeared.

It is of paramount importance to distinguish between the laboratory diagnosis of uncinariasis and the clinical picture of the disease. The presence of ova of this parasite in the feces is not evidence of the clinical entity now to be described; even ova in large numbers. True it is, that feces heavily laden with eggs are liable to pertain to an anemic individual, but this is not always so, as we have repeatedly seen great immunity enjoyed by some whites, and especially notable racial immunity of the negro to the effects of infection. Beyond a certain point, and in conditions of reduced vitality from lack of food or the presence of other diseases, this relative immunity may be, and often is, lost. The same immunity we have noted in the negro is said to be enjoyed by Asiatics. As a rule, however, heavy infections cause uncinariasis. Usually these infections are multiple and cumulative in their effects on the host, and the anemia and other symptoms come on gradually. At times severe single infections cause an acute form of the disease. All depends on the relative number of larvæ in the infected earth, a factor dependent on density of a population which practices earth pollution; and the exposure of the skin to invasion, in tropical countries chiefly through bare feet. It is of little practical importance to attempt the determination of the minimum average number of uncinariæ that will produce symptoms, but generally the greater the number harbored by an individual, the more abrupt will be the onset, the more pronounced the symptoms, and the more rapid the course of the disease.

Thus we may speak of acute and chronic, mild and severe cases, with every gradation from one to the other; also of a chronic case becoming acute when additional infections take place. This latter occurrence is frequent in places like Porto Rico, where opportunities for constant infection abound.

SYMPTOMS, COURSE AND USUAL COMPLICATIONS.

Uncinariasis presents a most varied symptomatology and a full discussion of it can not be included here. We shall omit mention of symptoms of minor importance and interest. A month or so after one or more such infections the subjects become languid and mentally inactive. Indefinite, fugitive pains in the epigastrium annoy them and tenderness in the right hypochondrium may generally be elicited. Pain in the sternum and chest are commonly complained of and slight breathlessness after exertion and occasional palpitation of the heart are noticed. A febrile movement of from 37.5 C. to 38.5 C. (99.5 F. to 103.3 F.) is not uncommon, but it is apt to be overlooked. The preliminary symptoms are obscure and the patient sums up his ill-defined condition by stating that he feels unable to work.

Little by little the predominant feature of the disease, anemia, makes itself manifest. The fever disappears, the hemoglobin goes steadily down and the train of symptoms dependent, in part, at least, thereon, come sharply into prominence. Most of the vague initial symptoms become positive. Headache, vertigo, tinnitus aurium, a louder and louder hemic murmur, weakening of the pulse and dyspnea ensue until, with the hemoglobin below 30 per cent., or even 20 per cent., graver signs present themselves. The pains in the sternum are an almost universal cause of complaint at this stage. An ever increasing debility and a more pronounced mental hebetude are noticeable. The patellar reflexes are generally reduced and later may even be abolished, and paresthesias of the lower extremities are common.

Impotence in the male and amenorrhea in the female are constant and striking phenomena in severe cases and are by no means rare in moderate ones.

A very little more and the patient reaches that point where even the result of anthelmintic treatment is problematic. We now have before us a very sick patient. The circulatory system is profoundly affected. The heart, slightly hypertrophied at first, is now not only weakened but is often dilated, a condition adding to the already complicated picture the familiar lines of a broken compensation. Edema of the feet and legs and puffiness of the face now become a general anasarca, and pericardial, pleural and peritoneal effusions are apt to take place. The hemoglobin falls below 30 per cent., even to 8 per cent., and the muddy yellow, pasty pallor eloquently testifies to its great reduction. The patient is bedridden, passive to his surroundings and gradually passes away as if narcotized, save that in the fatal cases of acute cardiac dilatation, cerebral effusion or violent diarrhea supervene, not uncommon accidents in our experience.

THE DIGESTIVE SYSTEM.

Although at first digestive derangement is fairly constant, evidenced by nausea, gnawing pain or weight and fullness in the epigastrium, a capricious appetite and constipation, it is rarely severe and sometimes little noticed by the patient. Once the anemia is established it is completely overshadowed by circulatory symptoms, if, indeed, the individual does not entirely disclaim any symptoms referable to the digestive apparatus at this stage. Nausea, however, is frequent and may be due to indigestion or to vertigo of cardiac origin. Vomiting is distinctly rare, but flatulence, pyrosis and meteorism are nearly always present. Constipation is common until the later stages are reached, when it alternates with diarrhea. The stools frequently contain mucus, but blood, in our experience, was rarely found, even microscopically.

Some writers have called attention to purplish spots on the tongue and have attached considerable importance to them as being distinctive of this disease. We have noted two kinds of discoloration: a rather diffuse smear generally on each side of the dorsum of the tongue, which apparently is due to venous engorgement and was not present in the majority of cases; and, rather more frequently, pigmented spots, 2 mm. to 4 mm. (1-12 to 1-6 inch) in diameter, were seen both on the tongue and the buccal mucous membrane. They were more frequently noted in persons of mixed race and could probably be found in other diseases.

One symptom stands out with great vividness in relation to disturbances in the digestive system and it is an important factor in bringing about a common complication. We refer to the craving for a bulky food, even resulting in bulimia in some cases. The oft-cited geophagy of uncinariasis is to be classed with this phenomenon and is an effect of infection, not a cause, even though it might, rarely, add to the number of uncinariæ already in the intestinal canal. Over-stuffing of the stomach leads to dilatation of its walls, which is usually diseased, and gastric dilatation is well known to be a frequent condition in uncinariasis. Other complications are acute gastritis, entero-colitis and dysentery. The most dreaded complication was enterocolitis and it was always cause for a bad prognosis in an old person with chronic uncinariasis. The diarrhea was very intractable in grave cases and was often the mode of termination in our fatal ones.

THE CIRCULATORY SYSTEM.

Circulatory symptoms commonly follow, but sometimes precede those of the digestive tract. They soon become prominent and are one of the chief sources of suffering to the patient. Apart from those mentioned, there are some features of circulatory disturbance which merit special consideration: In the later stages the apex

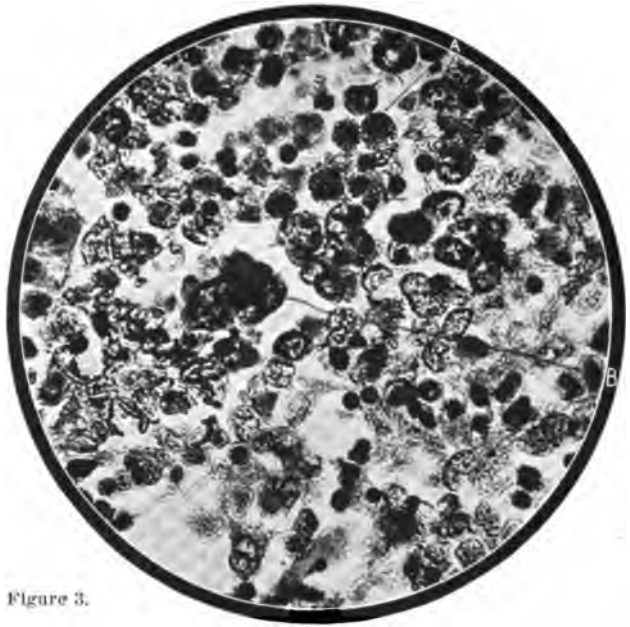

Figure 3.

Figure 4

Fig. 3.—Photomicrograph of bone-marrow in uncinariasis, × 750; A, group of eosinophilic myelocytes; B, myeloplax. By Dr. W. M. Gray.

Fig. 4.—Photomicrograph showing large phagocytic cells in blood channel of a hemolymph gland in uncinariasis. These cells have engulfed great numbers of red cells; × 750. By Dr. W. M. Gray.

beat may be replaced by a wavy, indefinite pulsation or a tumultuous heaving of the whole precordium. The heart's overaction is early manifested by pulsation in the vessels of the neck and, later, the tremendous throbbing in the supraclavicular spaces is one of the striking features. Pulsation in the jugulars was not infrequent and we have seen one instance of this condition in the brachial vein.

Few patients reach even a moderate degree of anemia without the production of a hemic murmur. An impure first sound and accentuation of the second may be the only signs in mild cases. Later it becomes a pronounced murmur, loud and harsh, best heard at the third left intercostal space. It is often the last sign to disappear under treatment, and indeed, in long standing cases, it may become permanent, due to organic change. On various occasions we had opportunity of seeing persons without anemia, the subjects of organic cardiac lesions, who gave a clear history of having suffered for many years in early life from severe uncinariasis. There is great danger of acute dilatation of the heart, even when convalescence is well established and the patient usually succumbs in a short while, although we have had cases of this kind in which the patient recovered completely.

THE NERVOUS SYSTEM.

Headache is almost invariably present, generally temporal and frontal; sometimes vertical or cerebellar. It may be severe before there is much circulatory disturbance. Susceptibility to cold is quite common, as is impaired tactile sensibility. There is dulling of the mental faculties even before the pallor and heart changes are noted. The listless indifference amounts at times to actual stupidity, with slow scanning speech and faulty memory. As recovery takes place, the change in the mental condition is one of the most pleasing results obtained. Familiarity with a large number of these sufferers leads one to recognize a characteristic facies as

typical as that of typhoid fever, or even more so. It is a melancholic, hypochondriacal, hopeless expression, certainly dominated by the mental state, but in a large measure enhanced by the edema of the face and the pasty pallor.

OTHER FEATURES OF THE DISEASE.

Edema is seldom seen before the hemoglobin has fallen to about fifty per cent. It is seemingly dependent on faulty circulation and blood and arterial changes and it may appear and disappear in a remarkable manner. In severe cases it always occurs at some time or other during the course of the disease. Anasarca is a late condition and, in grave cases, may reach an extreme grade.

The skin is usually dry and harsh. Even hard labor under the tropical sun may not induce sweating or, if so, only very scantily. Many of our more observing patients commented on the return of perspiration as indicative of improvement. In long continued cases there is actual atrophy of the skin, especially that of the face, giving a prematurely old and weazened appearance to a young person. Muscular weakness appears early and may become so extreme that standing is impossible. The muscles are flabby and tender, and they tire easily. The kidneys are generally the seat of chronic pathologic change, evidenced by albumin and casts in the urine. The albumin, which is small in amount, requiring very delicate tests to demonstrate, often disappears for a time only to reappear. It may or may not disappear permanently under treatment. Casts, hyaline, granular and fatty, do not always accompany the albumin and are seldom seen in large quantities. Both become very abundant with the addition of blood casts, if acute parenchymatous nephritis supervenes, as it did in several of our cases. Uremia may be the cause of death.[1]

1. A fuller discussion of the changes in the urine in uncinariasis will be found in a paper by the authors which appeared in the Boston Med. and Surg. Jour., April, 1907, clvi, 14.

In extremely edematous patients, edema of the lungs and ascites may prove very troublesome, even fatal, and we lost some of our patients, apparently, by a sudden edema of the brain. Attention has been called by A. W. Calhoun to the relation of uncinariasis to cataract. We found it prevalent in Porto Rico, especially in children and young adults. Night-blindness is relatively common, neuroretinitis occurs and retinal heromrhages are not rare.

Pregnancy is a grave menace to a very anemic woman. Abortion, premature labor or miscarriage are frequent results, though it is surprising sometimes how anemic a woman may be and yet carry the child to full term. Children born of anemic mothers are apt to be poorly developed and liable to marasmus. A still more pernicious effect on children is seen in uncinariasis which has dated back to early childhood and has for many years pursued a chronic course. Such children are stunted mentally and physically and at twenty years may seem to be not over twelve or fifteen, either in development or intelligence. While the disease is essentially a chronic one and of a very insidious onset, not rarely acute cases are seen. Here profound digestive disturbance, rapidly developing anemia and circulatory and nervous symptoms, with a tendency to edema and effusion into serous cavities, characterize the type.

The prognosis is generally good, even in severe cases, under appropriate treatment. Less hopeful are those complicated by persistent diarrhea, due to an enterocolitis, or other grave accident, especially marked anasarca from cardiac dilatation. To show, however, what results may occasionally be obtained by anthelmintic treatment, an example mentioned in our first report is worthy of quotation:

The patient's whole body was water-logged. She could hardly walk, could not see, the eyelids looked as if dry cups had been applied, and when her pulse was taken, the impression of the whole hand was left deeply sunken; yet she recovered and

became perfectly well, rosy and fat, running from 20 per cent to 90 per cent. hemoglobin.

Extremely low percentage of hemoglobin is not in itself an unfavorable sign. With a few exceptions, our cases of 10 per cent. to 15 per cent. responded readily to treatment; even some of 8 per cent. and 9 per cent. made complete recovery.

MORBID ANATOMY.

Despite the great amount of literature on uncinariasis in recent years, no subject is so barren of data as its pathologic anatomy, and yet this is decidedly one of its most interesting and instructive features. Not only are uncomplicated cases, suitable for the drawing of conclusions, difficult to acquire, but the consent of the relatives to autopsies is by no means easy to secure. Above all, deaths occur far out in the country, and usually before an autopsy can be performed, postmortem changes are well advanced. The latter obstacle was our most troublesome one, as the death rate in our field hospital was very small; indeed, it was but one-third of one per cent. for the entire number of 18,865 treated between May and December, 1905, at all stations combined.

In spite of these difficulties, eleven out of twelve autopsies were made in such manner as to furnish accurate information, in so far as the gross anatomy is concerned; nine supplied us with tissue in a very good state of preservation for microscopic study. The minute anatomy of the other two is not included on account of the length of time after death at which the autopsy was made. Of the nine specified above, one subject was five years of age and had never received any anthelmintics, one was fourteen, and the remainder between twenty-five and fifty. Six showed extreme anemia, one other was an intense case and two more were moderately severe. Only two were complicated by other conditions; in one a healed lesion of pulmonary tuberculosis was

found; the other presented the intestinal lesions of amebic dysentery. Nothing was shown in the latter to invalidate our conclusions.

GENERAL OBSERVATIONS.

As a rule, the body shows no emaciation and the amount of adipose tissue is apparently normal. There is not only much edema but all soft parts, including skin, muscle and internal organs, have suffered great change in color due to the intense anemia. The skin and subcutaneous tissue are very pale and sodden with fluid. The muscles are brownish gray, friable and often atrophied. On microscopic section the individual muscle-cells are frequently separated and the protoplasm seemingly starved and reduced in amount, an observation which, indeed, applies to nearly all organs.

On opening the abdomen, an excess of pale yellow or straw colored peritoneal fluid is observed, the amount reaching enormous quantities in certain cases where ascites is a prominent feature. In one of our cases this serum was reddish yellow, but no adhesions or other signs of inflammation were found. Serous effusion is also generally demonstrable in the pleuræ, pericardium and, sometimes, in the cerebral ventricles.

THE HEART AND LUNGS.

There was often hypertrophy, although, not rarely, a heart of normal size was encountered. It was not unusual to see an excess of pericardial fat. Not uncommonly, however, dilatation had occurred and the organ was remarkably flabby and easily torn. Microscopically, in two of three autopsies, brown atrophy was well marked and a slight degree of myocarditis was discovered. Fatty degeneration of the muscle fiber was clearly seen in two cases after fixation of the tissue by Fleming's solution. The separation of individual cells was particularly noticeable and this was irrespective of the fixing reagent employed.

The lungs were frequently the seat of edema and passive congestion.

THE LIVER.

This organ was practically never normal. Great increase in size was only once discovered, although never was there diminution. Its most frequent color was a light brownish yellow. In some cases it was very light yellow, soft and greasy to the touch and extremely friable. Microscopic sections demonstrated that it was often extensively affected in uncinariasis. Extreme fatty degeneration was the prominent feature of four cases and in two scarcely a normal liver cell could be found, the condition of the liver here simulating marked types of fatty changes in other diseases characterized by such changes. In none of our autopsies was fatty degeneration absent. In its least exaggerated form it chiefly affected the outer third of the lobule.

In three cases there was increase of connective tissue in the portal spaces, but in two of them the change was only slight, and, in at least one, where there was great increase, the condition was probably due to chronic alcoholism. Connective tissue increase is evidently not a feature of uncinariasis. Daniel's observation that the liver contains considerable yellow pigment could not be confirmed, save in one case, although small amounts were found in others. The pigment was not stainable by potassium ferrocyanid. Extreme dilatation of capillaries was found in two cases.

THE KIDNEYS.

These organs were also profoundly involved. They were very pale and were apt to be slightly enlarged. As a rule, the capsule stripped easily. Microscopic sections showed us a practically constant picture of chronic parenchymatous or chronic diffuse non-indurative nephritis. In persons of middle age, who had suffered for some years from uncinariasis, there was increase in connective tissue, but this was marked in only one case.

Usually, there was little or no connective tissue increase and polymorphonuclear leucocytes were conspicuous by their absence.

Changes were always found in tubules and glomeruli, but the convoluted tubules suffered most severely and fatty degeneration and desquamation in them was marked. The collecting tubules were much less affected. There was extensive exudation into Bowman's capsule with desquamation of its endothelial lining and much dilatation of the intracapsular space. Hemorrhages into Bowman's capsule, intertubular hemorrhagic areas and blood and epithelial casts, were found in four of the nine bodies sectioned, and the picture was that of an acute condition superimposed on the usual chronic one described. All four of these had received betanaphthol. In one case, yellow pigment was found, but only in small quantity. In two instances embolic abscesses existed.

STOMACH.

It was not usual to encounter uncinariæ in the stomach, although 83 were found in its lumen in an autopsy previously reported by us.[2] We discovered several adherent to the wall of this organ in this year's series. A gastric catarrh was common and marked dilatation was noted in two subjects.

INTESTINE.

The jejunum contained most of the uncinariæ found at autopsy. Some were unattached, others were adherent to the mucous membrane. In the first part of the duodenum were to be found most of the rest, a few being discovered in the ileum. None were encountered in the colon.

In more than one instance the parasites were alive twelve to fifteen hours after the death of the patient, whether attached or free. They were rarely red, gener-

2. Amer. Med., Sept. 5 and 12, 1903.

ally white or grayish. On one occasion they were removed with some little force by fine forceps and placed in physiologic salt solution, where they lived and remained active for about sixty hours longer and then were killed for experimental purposes.

The lesion of the intestine is confined, as far as we know, to the mucosa. It was found to be a tiny superficial erosion, not a deep ulcer, as many suppose, about 0.5 mm (1-50 inch) in diameter and not usually characterized by any redness, save at one autopsy. These erosions were very difficult to find without a hand lens, unless a parasite had just been removed from its feeding ground, and the locality marked. The duodenum, and especially the jejunum, are the seats of a chronic intestinal catarrh and many times after we supposed that all parasites had been removed in the course of the examination of the intestine at autopsy, many more were found buried in the thick mucus which more or less completely covered them.

The rest of the intestine, and even the colon, is apt to share in less degree in the general chronic inflammation. Degeneration and atrophy of the mucosa of the intestine, as well as of the stomach, were commonly observed. We have purposely left to the last a consideration of the really striking changes in the spleen, hemolymph glands and bone marrow, as these are marked and, until now, neglected in all treatises which we have read on uncinariasis.

THE SPLEEN.

Most authors state that the spleen is not enlarged, but lead us to believe that it is normal. As a matter of fact, the spleen frequently is reduced in size, soft, and possesses a wrinkled capsule.

Dr. Rafael Cesteros, of Guayama, Porto Rico, the director of the commission's substation in that city, reporting on one autopsy, writes of this organ as follows:

The atrophy of the spleen attracted my attention. It was as small a spleen as I have ever seen in my professional career and at no autopsy, whether made for scientific or for medico-legal purposes, have I encountered this organ of such reduced dimensions. Its color was that of wine lees and its size was not greater than that of the kidney.

Microscopic sections revealed in every one of the eight autopsies in which a portion of the spleen was preserved, a great paucity of lymphoid elements, even decided decrease in the protoplasm of the cells. The Malpighian corpuscles were greatly reduced in size, the cells were scanty and widely separated, and the central artery presented, almost uniformly, considerable hyaline degeneration. Not only were the tufts smaller than normal but they seemed fewer in number.

The apparent increase in connective tissue we explain by the decided reduction in lymphoid elements and blood, and it seemed relative rather than absolute, although in some instances, thickening of the capsule was observed. Pigmentation was only once very prominent, and the pigment was of the same character as that seen in the liver. There was unusually little blood in the organ.

HEMOLYMPH GLANDS.

The following notes were made by us at one of our autopsies:

Great abundance of glands in the region of the abdominal aorta was noted, especially at its bifurcation. They were enlarged, and of a dull reddish hue, like pale muscle tissue. Some of these glands were as large as hazel nuts, yet there was not a trace of inflammation in the surrounding parts and the peritoneum over them was normal and glistening.

They were only sought for in one other autopsy and then were found with the same characteristics, but in smaller number. Microscopic section showed that they were hemolymph glands, usually of the type described as splenolymph glands. Mitoses and phagocytoses of red cells were noted.

BONE MARROW.

The marrow of the midpoint of the shaft of the femur was examined in two autopsies. It was gravish red and very soft. Microscopic section disclosed, in addition to the changes described in the marrow of subjects dying of pernicious anemia, groups of eosinophilous cells, generally myelocytic. These cells were abundant, as were myeloplaxes. No attempt has been made to describe in detail the changes to be found in the organs referred to in this brief summary.

THE ANEMIA.

The anemia of uncinariasis is not merely such a condition as would result from repeated small hemorrhages. One of its marked peculiarities is its irregular eosinophilia and another is its severity at times in subjects harboring but few parasites, at others its failure to become marked in very heavy infections.

HEMOGLOBIN.

The average hemoglobin in 579 cases, taken at random before treatment, from among our 1904 series, was 43.09 per cent. Eight per cent. has several times been registered by both the Dare and the von Fleischl instruments. Fifteen to 20 per cent. was very common in severe cases and 35 to 50 per cent. was generally the range of moderate ones. The hemoglobin percentage is the steadiest guide to the condition of the patient, as a very low percentage may exist with a fair number of red cells, 0.5 being about the average color index.

Some phenomenal rises in hemoglobin were noted after simple expulsion of uncinariæ without any ferruginous or other regenerative treatment, rises which seem impossible were it not for the fact that fully as remarkable improvement takes place in the patient himself, the gain in healthy color testifying to the actual return of his blood to normal. For example: In one case, a woman, aged 38, with a hemoglobin of 35 per

cent. on admission, there was a rise of 61 per cent. in 15 days, although but two doses of betanaphthol were given and 453 of the total number of 497 uncinariæ expelled.

We gradually learned that iron was not a necessary part of the treatment of uncinariasis, as a rule. Certainly a somewhat more rapid rise in hemoglobin occurred when iron was used, but the return to normal came about just as surely without it and we ceased to use it among our average cases, reserving its administration for obstinate ones in which blood regeneration

Treatment.	Betanaphthol weekly; iron in intervals.	Thymol weekly; iron in intervals.	Betanaphthol or thymol; no drug in intervals.
Number of cases	20	32	9
Average initial hemoglobin, per cent.	33	32.8	42.6
Average days under treatment	40	37.3	17.3
Average rise, per cent., in hemoglobin for time specified	51	52.4	28.3
Average number of uncinariæ expelled	1,064	1,264	591
Average rise hemoglobin per cent. daily	1.2	1.4	1.6

was faulty and all parasites had been expelled. Blaud's pills seemed to us the best form of iron, as stated in our 1904 report, but it is a matter of but little importance, in the end.

In these cases of tardy rise of hemoglobin there was apt to be a period of about two months in which no marked increase was noted, when in the succeeding month the normal was reached by rapid strides. In others the hemoglobin rose steadily without being hurried in the least by large doses of Blaud's pills.

The above résumé of sixty cases in our 1906 series, is of interest in this connection. They are cases of patients in whom the hemoglobin was estimated on admission and discharge, and the actual number of uncin-

ariæ expelled after each dose of the anthelmintic was determined. Twenty are cases of patients to whom betanaphthol was given weekly, with daily doses of iron in the intervals; thirty-two received thymol weekly and iron in the same manner; and nine received thymol or betanaphthol without the use of any drug in the interval. The patients were not always held in the hospital until the hemoglobin became normal, because an expulsion of all parasites was almost certain to be followed by the cure of their anemia, a fact abundantly demonstrated to us in the thousands of other cases under treatment as outpatients, and by our past experience.

Attention is invited to the fact that the cases treated without iron were less severe, as a rule, and that this alone explains why, with better recuperative power, the blood making organs were enabled to cause a greater daily rise in hemoglobin. Nevertheless, the advantages of iron, in average cases of moderate severity, are not seen to be very great. A fall in hemoglobin is the first sign of the anemia and this fall may be considerable, even as much as to 30 per cent, before the erythrocytes are greatly reduced in numbers. On the other hand, the rise in hemoglobin almost always lags behind the rise in red cells under treatment.

ERYTHROCYTES.

In our 1904 series of 61 cases in which weekly blood counts were made until the normal was reached, 2,406,416 erythrocytes per c.mm. was the average. The lowest count made was 754,000 per cmm. There was polychromatophilia and, in severe cases, poikilocytosis with many macrocytes and microcytes. Normoblasts and megaloblasts were not uncommon, but the latter are generally much in the minority.

LEUCOCYTES.

There is no leucocytosis which is constant, but slight increase in leucocytes is at times seen, especially in acute cases. In chronic cases there is apt to be leucopenia.

Our average white cell count was 8,009 per cmm. on admission. In making differential counts, 250 leucocytes were classified, and in this connection we wish to emphasize the decided tendency of leucocytes to degenerate. Stimulation cells of Türck were frequent in some cases, but their appearance was very uncertain and we were unable to assign any special significance to them. Myelocytes, generally eosinophilic, were seen occasionally, but were not common.

Eosinophilia is the chief feature of importance. It is strange that Boycott and Haldane lay so much stress on the importance of eosinophilia, from a diagnostic point of view, for in the more serious cases it is liable to be absent. In 1904 we called especial attention to our belief that eosinophilia was of great prognostic importance and have noticed that some German and Spanish writers subsequently express this same view. Very chronic cases, of severe type, poor resisting power, and lack of blood regeneration, rarely show eosinophilia, or, if at all, only to a slight degree. A rise in eosinophilia is of good prognostic significance and their fall, with lack of improvement in the symptoms, is not a good omen. In general, good resistance to the hypothetical toxin of uncinariæ is expressed by eosinophilia.

TREATMENT.

The prime object of treatment is to expel the uncinariæ, and our choice of the anthelmintics will naturally be the one most rapidly and easily effecting this result.

We attempted to ascertain the relative efficiency of male fern, thymol and betanaphthol by counting the actual number of uncinariæ expelled by each dose. During the twenty-four hours following the administration of the drug, all the feces evacuated by the patient were passed into an individual vessel and treated with a 10 per cent. formalin solution, which destroyed, in most instances, practically all offensive odor. As a rule, the

evacuations were liquid, but if not, water was added. The twenty-four hour feces were strained through cheesecloth and thoroughly washed. The residue, which usually was small in quantity, was transferred with a porcelain spoon to a small dish or cup, care being taken to pick off with forceps any worms remaining on the cloth. The counting was done in a trough of convenient size, made by nailing a narrow strip on each side of the board and painting the inside black. A small quantity of the fecal residue was placed in the trough and water was added, a few drops at a time, washing it away bit by bit, the trough being inclined barely sufficiently to cause a flow. The worms can be easily detected against the black surface and be picked out by forceps. Care must be taken that the water is not added too rapidly or some of the worms may be washed away. Lumps of feces should be broken up and all fragments of food, etc., inspected for adherent worms. While hardly esthetic, these operations are seldom particularly offensive.

The results of our counts were interesting and instructive except those in cases where male fern was given. We used first an ethereal extract of this drug from one of the most reputable German pharmaceutical laboratories, but although it caused constitutional symptoms, practically no uncinariæ were expelled by it. As we had purchased the drug from a local pharmacist, we thought that possibly it had been some time in the tropics and had become deteriorated from climatic influences, to which it is said to be very susceptible. A fresh solid extract was then obtained direct from one of the best known pharmaceutical houses. It was immediately put into use, with no better results as an anthelmintic, although the constitutional effects were much more marked than those of thymol or betanaphthol.

The highest number of uncinariæ expelled by a single dose of either of these preparations of filix mas was eight, while one of the same patients later expelled 3,686

uncinariæ after a single dose of three grams of thymol. So much time had been spent in these unfruitful trials that had we ordered other preparations of the drug, we could not have completed a series of counts owing to the short time left for the completion of our work. Considering the success which has followed the use of male fern in Germany, we are at a loss to understand why we should have scored such a failure with it, unless this drug very rapidly becomes worthless in warm countries.

In testing these anthelmintics, our intention was to administer them at weekly intervals and to continue for two weeks after uncinariæ ceased to be expelled. We found that it was often impossible to hold the patients in hospital long enough to do this, because by the time they had expelled most of their parasites, they felt so much better that they insisted on going home, and if denied permission to do so, would desert. Hence we were obliged to throw out many counts as incomplete, but we did include those in which less than twenty uncinariæ were expelled by the last dose given, even though there was no opportunity to administer later doses, which might have brought away a few more in some cases and none in others. This slight inaccuracy does not materially affect our results.

In the preliminary report, 1905, of the Anemia Commission, is published a table giving the number of uncinariæ expelled by each dose of betanaphthol. Reference to this table will show with what heavy infections we were dealing; the lowest being 73, the highest 4,395, and the average 1,027. The amount of anthelmintic is not stated, as it varied even in the same patient at different times. The dose had to be based on the age and condition of the patient, and thus the table represents the actual results obtained by these vermicides when properly used in practice. The following figures express the comparative percentages of the total number of uncinariæ expelled by each of these drugs in 70 cases:

PERCENTAGE EXPELLED OF THE TOTAL NUMBER OF UNCINARIAE HARBORED BY THE INDIVIDUAL.

Dose.	Average of 40 patients treated with thymol.	Average of 30 patients treated with betanaphthol
1	76.85	72.24
2	92.89	88.12
3	97.55	93.67
4.	99.06	96.57
5	99.80	98.71

Some time after these counts were begun it was discovered that, at times, all the uncinariæ killed by the anthelmintic would not be evacuated during the first twenty-four hours, even though there had been free purgation, but that others came away in the second and, more rarely, the third twenty-four hour period. Thus Boycott and Haldane are mistaken in supposing that after the twenty-four hours the dead uncinariæ are digested. No doubt some of them are, as we found partially digested ones, but we think their statement too sweeping. Had we recovered all the worms appearing on the second and third days, we would have recorded a slightly greater number expelled, particularly after the first and second doses, but the percentages of results would have been changed scarcely more than a fractional part.

There is a surprising equality of anthelmintic effect after five doses of either drug, though thymol shows a somewhat greater rapidity under equal conditions of proper preparatory treatment. However, when the preliminary purge and, more especially, the abstinence from solid food for a day are omitted, betanaphthol shows much less favorably. We used some hundreds of pounds in the out-door clinic, the patients taking the medicine after returning to their homes. They generally took the purge, but the directions to abstain from solid food were more honored in the breach than in the observance. Many of those to whom betanaphthol was given kept returning week after week and at each time revealed ova of uncinariæ in the feces. In other words, the presence of food in the bowel seemed to interfere with the effi-

ciency of betanaphthol more than of thymol, for those who took thymol in their homes expelled their parasites almost as rapidly as those whose diet we could supervise. Frequently in these resistant cases a dose or two of thymol caused a complete disappearance of ova from the stools, while increased doses of betanaphthol did not have so marked an effect.

Betanaphthol is not only less efficacious, but it is more dangerous. It has, at times, an irritant effect on the kidney, setting up an acute toxic nephritis in an organ so often the seat of chronic parenchymatous changes. This effect was not common, but the accident was so serious as to warrant our return to thymol as a much safer vermicide. Thymol on rare occasions may irritate the kidney, but its effect is much less severe. It may produce, infrequently, more or less severe collapse. The chief objection to its use was its irritating effect on the bowel and several times, we believe that enterocolitis has been initiated by its administration.

Eucalyptol is now being studied by the present commission, but their report has not yet been made. Both thymol and betanaphthol were administered in the same manner except that one-half as much betanaphthol was used at a dose as thymol. Betanaphthol in larger doses did not seem to give proportional results.

The patient was required to abstain from solid food during the day and at night 25 grams of sodium sulphate was given. The next morning, providing free purgation from the salts was secured, after a glass of hot milk or on a fasting stomach, one-half of the anthelmintic was given and repeated in two hours, followed, about noon, by another purge which may be omitted if the bowels are moving freely. This procedure was repeated each week until ova disappeared from the feces.

We have given thousands of doses of thymol without having known of a case of poisoning from it, notwithstanding that at times, we knew that, contrary to our orders, alcohol in some form had been taken to relieve

the dizziness and other disagreeable effects sometimes produced by thymol in large doses.

In choosing the anthelmintic we have to be governed somewhat by the circumstances of the case, condition of the patient, and so forth, but, all things being equal, we decidedly prefer thymol for general use. When it is not possible to use it, betanaphthol is an excellent substitute. The taking of either is unpleasant and, naturally, we want to use that one which the least number of doses need be taken to obtain the greatest result.

Our thanks are due to Drs. Carroll, Russell and Gray of the laboratory of the Army Medical Museum and Dr. Rosenau of the Hygienic Laboratory, Washington, D. C., for many courtesies extended us in our work on the morbid anatomy of uncinariasis and acknowledgment is made of painstaking services rendered by First Class Sergeants Neat and Britton, Hospital Corps, U. S. Army.

THE DIAGNOSIS OF ANEMIA.

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We may be concerned either with the fact, or with the type. Is anemia present? If so, what kind?

The question whether or not anemia is present can be decided only and sufficiently by testing the hemoglobin. We should never assume that anemia is present either from the symptoms alone, or from the appearance of the patient, or from both taken together. Mistakes from this cause are many. On the other hand, there can be no mistake in supposing that the patient who has a low hemoglobin is anemic, and practically no mistake in supposing that the patient whose hemoglobin is normal, or nearly so, is not anemic.

Diagnoses of anemia are very much more frequent than the facts justify. Patients are frequently treated for anemia when nothing more than a pale skin substantiates the diagnosis. The treatment does no harm except in so far as it may prevent us from taking measures more appropriate for whatever disease does genuinely exist. On the other hand, the mistake of assuming that a patient is not anemic, because there is a good color in the face, may lead to more serious consequences.

When the hemoglobin is normal, then, we need go no further in our blood examination, and may rest satisfied that anemia is not present. If the hemoglobin is low, we must endeavor, both by a general physical examination and by a study of the blood, to determine what type of anemia is present.

The important types of anemia may be classified as follows:

1. Chlorosis.
2. Pernicious anemia.
3. Secondary anemia, including:
   (a) Parasitic types.
   (b) Other types.

Rarer varieties are:

4. Myelophthisic anemia.
5. Aplastic anemia.

The first two types mentioned above are distinguished from the others by the fact that we have no idea of their cause. In this sense they may be and have been called "primary." The other types of anemia are "secondary" in the sense that they would not exist but for the presence of other diseases of one or another organ.

In the practical work of distinguishing these types of anemia the history of the case is of value to us chiefly when it points to some disease to which we can attribute the anemia as a result. If there is a history of recent malaria, dysentery or hemorrhage, this is important, though not conclusive, evidence that the anemia belongs to the type called secondary. If the history gives presumptive evidence of the presence of malignant disease, of nephritis, or syphilis, it may afford us a useful hint regarding the type of anemia present. But so far as the symptoms of anemia itself are concerned, they are quite indistinctive and almost useless to us in differential diagnosis, because they do not differ essentially from those which may be produced by cardiac disease (organic or functional), or by a variety of debilitated states. The pallor and weakness, the dyspnea, the stomach troubles, the slight edema of the ankles, the throbbing arteries and disturbed sleep are all non-characteristic of the anemia to which they are due, because perfectly similar symptoms may be produced by other diseases.

On the other hand, considerable aid is given us by taking account of the age and sex of the patient and

by taking a good look at him. Thus anemia existing in a girl between 17 and 25 is generally of the type known as chlorosis, while severe anemias in persons past 45, who do not complain of any special local symptoms but chiefly of general weakness, are very apt to turn out pernicious.

It is, therefore, on the physical examination of the body generally, and the blood in particular, that we must depend for definite diagnosis. To this subject I now turn.

The most important differential point in the physical examination of cases found to be anemic is the determination of the presence or absence of some organic disease known to be capable of producing anemia. On the other hand, a negative physical examination, including a negative examination of the urine, is a most important piece of information. Provided we know that anemia is present, a negative physical examination in a young girl points strongly to chlorosis, and in a person past 40 points strongly to pernicious anemia. I do not think there is any type of anemia which can be positively determined by the blood examination alone. Consequently, in the description of the different types to which I now turn, I shall group together all symptoms, physical signs and hematological data, which together determine diagnosis.

I. CHLOROSIS.

There is no such thing as chlorosis in boys, and if it occurs in a woman past 30 it is almost invariably a relapse or recurrence of a chlorosis established earlier. The typical age, as has already been stated, is from 17 to 25, that is, during the years immediately succeding those in which the function of menstruation is established. Though the patients complain of weakness, dyspnea and the other symptoms common to all anemias, they are usually not emaciated, but rather plump. Physical examination is negative or shows nothing

more than systolic murmurs at all the valvular orifices of the heart, with perhaps slight edema of the ankles. The menses are often suppressed, and dyspepsia in one or another type is almost always present. The blood shows a reduction of hemoglobin to a point which averages 40 per cent. of the normal, while the red cells are not far from the normal point, averaging about 4,000,000 to the cubic millimeter. This discrepancy between the reduction of red cells and the reduction in hemoglobin means that each cell contains only about half the amount of hemoglobin present in a normal red cell. This fact is technically known as a "low-color index," and is further revealed in the stained film by the striking pallor of the centers of the corpuscles and the general tendency to a diminution in the diameter of the cells. There is nothing remarkable about the white cells. The disease seems to be getting rare—rarer than pernicious anemia.

II. PERNICIOUS ANEMIA.

The onset of this variety is strikingly insidious. Patients can rarely tell within a year or two when it was they began to feel the general weakness and incapacity for the relief of which they seek advice. There are usually no striking local symptoms, and physical examination in the early stages of the disease may be absolutely negative. It is only relatively late that we see the pale yellow tint of the skin, or find any changes in the function of the spinal cord. Patients are usually well nourished, for their digestive functions are rarely disturbed except for relatively short periods of time. The red cells are usually reduced to 2,000,000 or less at the time the patient first consults a physician. This reduction is in striking contrast to the absence of severe pain or other local symptoms. The hemoglobin is usually reduced relatively less than the number of corpuscles, that is, with a count of 2,000,000 red cells we may have 50 per cent. of hemoglobin. The white cells are usually subnormal. In the stained specimen we see that each cell

contains as much hemoglobin as it ought. There is no pallor of the centers and the cells are strikingly oversized. This is the most important single point in the diagnosis of the disease. Less important are the great deformities, the changes in staining reaction, or the presence of nucleated red corpuscles.

This blood picture is not absolutely characteristic of the disease, but, when taken in connection with the history and the physical examination as above outlined, it is almost pathognomonic.

The diseases most likely to be confused with pernicious anemia are cancer of the stomach, myxedema, nephritis, cardiac disease and one or another of the parasitic anemias. Each of these will now be discussed, as types of secondary anemia.

III. SECONDARY ANEMIA.

1. *Malignant Disease and Pernicious Anemia.*—In the vast majority of cases malignant disease produces no anemia that is at all likely to be mistaken for pernicious anemia, but now and then we see cases, especially of gastric cancer, in which the count of red corpuscles will not distinguish the two diseases. Here the presence of marked and especially of continuous digestive troubles, together with a considerable degree of emaciation, a low-color index, and the presence of small-sized, poorly-stained red cells, with relatively few megaloblasts, or none at all, points to cancer of the stomach. Of course where a tumor can be felt the difficulty of diagnosis is not likely to arise. If, on the other hand, the patient is relatively well nourished, has periods of weeks or months during which digestion is good, and if the blood shows a high-color index and large-sized red cells—greatly deformed, abnormally stained and often nucleated—the disease is probably pernicious anemia.

2. *Myxedema.*—A clinical history and picture identical with that of pernicious anemia may be found in myxedema, except as regards to the data afforded by

blood examination. The age of the patient, the insidious onset, the good nutrition, the general symptoms of anemia, the digestive disturbances (occasional, not continuous), may be the same in both diseases. But here the blood examination sets us right, for the blood of myxedema is never strikingly similar to that of pernicious anemia, but presents the characteristics of other types of secondary anemia, as described in the last paragraph.

3. *Nephritis.*—Only the external aspect of the patient and the general complaints are confusing here. The blood is quite unlike that of pernicious anemia, and the examination of the urine should help us to a speedy differentiation of the two diseases. It should be remembered, however, that pernicious anemia can and often does coexist with a considerable degree of those senile changes in the kidney which receive the name of interstitial nephritis when they become extreme. This coexistence of the two diseases should not be interpreted as anything more than coincidence. The nephritis is in no sense the cause of the anemia, for in the vast majority of cases this type of nephritis runs its course without any anemia whatever.

4. *Cardiac Disease.*—This malady is similar to pernicious anemia only in the symptoms which it presents, and sometimes in the pallor which accompanies it—a pallor due presumably to the imperfect filling of the subcutaneous blood vessels. The absence of any considerable anemia easily distinguishes the two diseases as soon as the hemoglobin test is made.

5. *Myelitis*—Diffuse or patchy sclerosis of the spinal cord accompanies a large proportion of all cases of pernicious anemia. In some of these cases the cord symptoms are so prominent and the symptoms of anemia so mild that the diagnosis of myelitis is made—the anemia being altogether overlooked. The blood examination, however, is usually as characteristic as in the cases without cord symptoms, and if we do not forget altogether

to examine the blood the diagnosis is easy. The importance of differentiating simple myelitis from pernicious anemia with cord changes lies in the fact that the latter usually runs a much shorter course than the former.

6. *Parasitic Anemias.*—The fish tapeworm (*Dibothriocephalus latus*) is often carried by an individual without any anemia resulting. In other cases the blood is more or less diseased, and in a considerable group the blood may be absolutely identical with that of pernicious anemia, as has been shown by the minute and careful studies of Schaumann among the Finnish fishermen.

Hookworm disease, on the other hand, while often producing a very severe type of anemia, rarely produces a blood picture similar in all respects to that of pernicious anemia, for in hookworm disease, even when the red corpuscles are reduced to 1,000,000 or less, the color index usually remains low, the corpuscles small or of normal size, palely stained and less deformed than in pernicious anemia. Abnormal staining reactions and the larger types of nucleated red cells are less frequent, while the increase of white cells, and especially of eosinophiles, is usually distinctive.

In both the parasitic anemias just described, however, an examination of the feces is the mainstay of diagnosis, for in cases severe enough to produce a profound anemia the eggs of the parasites responsible for the disease are sure to be easily found.

IV. MYELOPHTHISIC ANEMIA.

As a result of a leukemic overgrowth of white cells in the bone marrow, as in the latter stages of leukemia, the red-cell-forming tissue of the marrow is apt to become so much compressed that a pressure atrophy occurs. As a natural result of this the supply of red corpuscles sent out into the blood stream becomes progressively diminished, and a grave anemia develops. This happens in almost every case of leukemia, both of the so-called lymphatic and the so-called myelogenous

type, provided the patient lives long enough for the development of the pressure atrophy above described. In conditions other than leukemia, myelophthisis anemia is not often seen, but a few cases have been recorded resulting from malignant disease affecting the bone marrow.

The diagnosis of this type of anemia must depend wholly on its cause, that is, on the recognition of an overgrowth of cells of one or another variety, which drive the red-cell-forming tissue into a corner. This means in most cases the recognition of the disease leukemia, one of the easiest of all diseases to recognize.

In practical diagnosis, therefore, this type of anemia raises no considerable difficulty; it is here introduced merely because from the point of view of pathogenesis it deserves to be distinguished from the other varieties above described.

V. APLASTIC ANEMIA

Most of the recorded cases of this rare disease have occurred in young girls and have been accompanied by severe purpura. The blood is like that of pernicious anemia, except that the erythrocytes are smaller and rarely contain nuclei, while all the granular varieties of leucocytes are greatly diminished. Postmortem we find fatty marrow in the long bones, with no trace of regenerative effort.

ELEMENTS OF DIAGNOSIS IN ANEMIA.

	Chlorosis	Pernicious Anemia.	Secondary Anemia in General.	Parasitic (Secondary) Anemia.	
				Due to a Fish Tapeworm.	Due to a Hookworm.
Cause...	0	0	+	+	+
History..	Not helpful.	Not helpful.	Very helpful.	Helpful.....	Helpful.
General physical examination.	Not helpful.	Not helpful.	Very helpful.	Eggs in stools.	Eggs in stools.
Blood...	Small cell type.	Large cell type.	Small cell type.	Large cell type (sometimes).	Small cell type (usually).

SUMMARY AND CONCLUSIONS.

1. In the diagnosis of anemia it is essential to take account of all the facts in the case. The etiologic factors and the data of general physical diagnosis are as important as the hematologic findings. Especially is this true in the types of anemia known as secondary.

2. There are but two important types of anemia, if we are to distinguish by blood examination alone. To the first type (the small cell type) belongs the anemias secondary to hemorrhage, malaria, nephritis and other diseases which lead to increased destruction of red corpuscles. So far as the blood picture is concerned, chlorosis is identical with the types just mentioned. It is distinguished wholly by the absence of etiologic factors and by the age and sex of the patient.

3. Pernicious anemia usually, but not invariably, can be recognized by the blood picture alone. If the data of blood examination are combined with those obtained by a careful history and physical examination the diagnosis is one of the clearest and surest in medicine. The most important single fact in the blood examination is the great reduction in red corpuscles, with a relative increase in the amount of hemoglobin per corpuscle (large cell type of anemia).

4. The parasitic anemias are not always to be recognized by blood examination, but present no difficulties of diagnosis if the eggs of the responsible parasites are sought. Myelophthisic anemia is easily recognized by the evidences of its cause and offers no difficulties in diagnosis.

THE TREATMENT OF ANEMIA.

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I do not intend to read a paper on the details of the treatment of anemia. All are familiar with the chief measures and remedies employed in this treatment: Iron, arsenic, rest, nutrition, fresh air and other dietary and hygienic measures. As to the particulars, any of the many good text-books will give the desired information. But to do some justice to the task assigned to me, which at a weak moment I have thoughtlessly accepted, I shall discuss briefly some points in the treatment of anemia which, to my mind, mark a distinct progress. I do this with special pleasure, since the underlying work of some of these points was done in this country by men to whom the medical profession of this country owes a debt of gratitude for their continued splendid activities in the fields of science and practice of medicine.

The first point I wish to bring out refers to the progress made in the method of transfusion. In secondary anemias, especially in those following acute or chronic hemorrhages, the best measure of treatment of the anemia would be to replace the lost blood. But a century of attempts to carry out blood transfusion proved futile. Alien blood, or defibrinate blood of the same species, is harmful to the recipient, and the method introduced by Von Ziemssen, namely, the rapid withdrawal of blood by a syringe from the vein of a spender and its immediate injection, without defibrination, into the vein of the receiver, had very little success in prac-

tice. The method generally in vogue at present is, as you know, the venous infusion of one form or another of a so-called physiologic salt solution. Obviously these solutions do not replace the essential element of the blood, the red cells.

Within this year, however, the problem of transfusion has been brought nearer its solution by a bound, through the experimental and clinical efforts of George W. Crile. Using the improved technic of Carrel, he established an end to end union between a vein of a donor and an artery or a vein of a receiving animal, thus establishing a transfusion in which the blood of one animal is flowing directly into the vessels of another animal free from the dangers of intermediary manipulations. In a long series of experiments, that surgeon-physiologist has studied the effect of such a direct transfusion on the receiving animal and obtained most gratifying results. Even after complete exsanguination of an animal, with complete stoppage of respiration and with only a barely perceptible auricular heartbeat, a direct transfusion led invariably to a complete recovery of that animal. Crile next tested that method in a desperate post hemorrhagic case of anemia in a human being, brothers lent themselves as spenders, and obtained the same blissful result. In a recent communication before the Society for Experimental Biology and Medicine, Crile summarized his present clinical results by stating that the direct transfusion is a positive cure in all acute hemorrhagic anemias, and that in pathologic hemorrhages not only is the anemic condition invariably benefited but also the hemorrhages themselves are, in most instances, controlled without special treatment.

Permit me to point out that the experiments which that admirable man of Cleveland has carried out on seventy dogs will, undoubtedly, save thousands of human lives, and I feel called on to add that the so-called humane societies, which direct their agitation against animal experimentation and which just now, in their

libelous circulars, are dragging the good name of Crile into mire, are engaged in a criminal activity which moral men, and especially physicians, should strongly resent.

The second point I wish to bring out concerns a simple method of treatment of pernicious anemia based on an advance made in the understanding of its etiology. The pathology of this disease, which is also designated as primary or idiopathic anemia, is admittedly obscure, but it was generally assumed that the cause is probably within the blood itself. During the past few years several writers have advanced the view that the disease is caused by an infection or an intoxication from the gastro-intestinal canal. These surmises had not much significance, since no facts were available showing a connection between the anemia and some definite form of infection or intoxication. Recently, however, in a profound and extensive study of the chemistry of the feces and the urine and of the bacteriology of the feces of fifteen cases of pernicious anemia, Christian A. Herter made a discovery that within the intestinal tract of such patients certain specific putrefactions are going on which are caused by the activity of anaërobic bacteria and that the *Bacillus capsulatus aerogenes,* discovered by Welch, is greatly in evidence in the feces of these patients. With the recovery of the patients from their anemic condition the predominance of this anaërobic bacillus in the feces disappears. Here we have a definite, well-established fact that at least in a certain number of cases of pernicious anemia, the anemic symptoms run parallel to the presence of well-defined anaërobic bacteria in the intestinal tract, and are probably caused by them. Among other measures of treatment in these cases, Herter recommends frequent and thorough irrigation of the colon, since it is the chief thriving place of these bacteria. Following this suggestion, Dittmar and Hollis were able to report a few months ago cures in two cases of pernicious anemia by irriga-

tion of the colon which resisted all other methods of treatment. A few years ago Grawitz reported several cures of pernicious anemia treated by lavage, irrigation, restricted proteid diet of animal origin and other merely dietetic measures. It may be that lavage, as well as the restriction of the proteid diet, are unessential to the success. At any rate, the discovery that a good many cases of pernicious anemia are due to intestinal putrefaction, caused by anaërobic bacteria, and that some of these patients can be cured simply by efficient irrigation of the colon, present surely a valuable scientific and practical progress.

The third point I wish to touch on very briefly relates to the rôle of iron in the animal organism and its use in the treatment of anemia.

It is an old, well established clinical observation that inorganic iron is a most efficient remedy in chlorosis. For the last two or three decades, however, its use was opposed to and ridiculed by able physiologic chemists and pharmacologists on the ground that inorganic iron can not be assimilated or even absorbed. The history of the scientific struggle over this subject is very interesting and instructive, but I could not think of entering on it in the brief time allotted to me. I shall only say that, as I believe, the struggle is now decided in favor of the clinical position and that recent pharmacologic writers, at least the majority of them, fully admit that ingested inorganic iron is just as capable of being absorbed and assimilated as the organic iron compounds of the food.

In connection with the last-mentioned problem, I wish to state briefly my view of the relations of the ingested iron to the iron of the hemoglobin, a view which is based on well established clinical and experimental facts, as we know them at present.

The normal animal body commands a large reserve fund of iron which is far in excess over its immediate requirement. The liver, bone marrow, and espe-

cially the spleen, are the main depositories for the reserve iron, where it is preserved in the form of resistant organic compounds, like *ferratin,* for instance. All ingested and absorbed iron, no matter of what character and origin, goes first to one of these depots, where it becomes converted into the organic compounds; The first function of the absorbed iron is, therefore, to increase the iron reserve. The iron requirements of the blood are supplied from the organic compounds of the iron reserve, which becomes then converted into hemoglobin; the ingested iron, no matter of what character, is never utilized directly for the construction of hemoglobin. In normal conditions the iron requirement of the blood is small and presents a comparatively constant quantity, which varies but little with the size of the reserve fund of iron, provided the latter does not sink below a certain limit. The quantity of the reserve iron, on the other hand, is apparently capable of greater variation, but also only within certain limits. The greater ingestion of iron has therefore, in the normal animal, no influence on the conditions of the hemoglobin in the blood, as at best it swells only the iron reserve.

From the point of view presented here the metabolism of iron has certain features in common with the metabolism of carbohydrates. No matter in what form the carbohydrates are ingested, they are always deposited in the liver in the form of glycogen, where it exists in excess over the immediate requirements of the body, and from where the blood is being continually provided, after the conversion of the glycogen into sugar, with an amount just sufficient to keep up a certain constant quantity. Iron then, like the carbohydrates, is stored up in the body in the form of intermediary organic compounds into which all ingested materials are converted and all requirements of the body are drawn on.

In conclusion, I may perhaps be permitted to point out that iron is an indispensable constituent of the animal body and, in conformity with the law governing all

other bodily constituents, it is provided in considerable excess over the normal requirements of the organism; in other words, they are provided with factors of safety.

DISCUSSION

ON PAPERS OF DRS. BUNTING, ASHFORD AND KING, CABOT AND MELTZER.

DR. THEODORE POTTER, Indianapolis, said that he has noted the frequency of pernicious anemia in the rural districts. During the last year, for instance, out of five successive patients with pernicious anemia seen in a period of nine weeks, four came from the country. To be sure, the location may have something to do with it. Indianapolis, with its population of nearly 200,000, surrounded by a thriving farming community, has brought to it a good deal of consultation practice from that part of the country. Four out of these five patients came from the country, all men, between the ages of 47 and 55, all farmers. While that proportion is not always the rule, Potter has, for some time, been impressed with the rural prevalence of pernicious anemia. In the medical society it is a common thing to hear reported cases of chlorosis, factory and shop girl's anemia, leukemia, Hodgkin's disease and pernicious anemia, but it is noted that many of the cases of pernicious anemia come from the rural districts.

DR. A. D. ATKINSON, Baltimore, said that he had had a patient with uncinariasis who apparently recovered perfectly. The patient died of pulmonary tuberculosis, four years after treatment for hook-worm disease with thymol, and the autopsy showed no lesion in the intestinal tract.

DR. AUGUSTUS A. ESHNER, Philadelphia, declared that the papers read on this subject have done much to sweep away the attempted differentiation between primary and secondary forms of anemia, especially Dr. Cabot's classification. Dr. Cabot makes three tabulations of anemia, but he points out that the blood changes in chlorosis are practically the same as those in other forms of so-called secondary anemias. The distinction between so-called primary and secondary forms of anemia must disappear with constantly increasing knowledge. While some forms are due to obvious causes, others are of more obscure origin. Thus we recognize parasitic and other forms of anemia, but the causes of chlorosis and of pernicious anemia are at present beyond our scrutiny. As pointed out by Dr. Bunting, however, there is a reasonable probability, in a considerable group of cases at least, that the cause is a toxic one. In view of that fact, and especially in view of the blood findings, it seems that it would be wiser to make a classification based on the blood findings rather than on the etiology. Dr. Eshner proposed, accordingly, a division of anemias into qualitative and quantitative. The designation

qualitative may be applied to the type of pernicious anemia, in which there is a change in the relation between the number of blood cells and the percentage of hemolglobin, causing a low blood index, while the designation quantitative is applicable when there is a depreciation in both the hemoglobin percentage and the number of blood cells. A given specimen of blood may, of course, exhibit both quantitative and qualitative changes.

DR. WOODS HUTCHINSON, New York City, said that the more time spent in the study of cases of chlorosis, and the more careful examinations made from every point of view, the fewer cases will be found. He believes that we have been confusing other things with chlorosis, especially incipient tuberculosis. The more the anemias are studied the more will it be found that toxins of some sort played a part in their causation. The motto of a celebrated detective when assigned to a case was "*Cherchez la femme*," "Look for the woman." In the anemias, our motto should be "Look for the toxin," whether of endogenous or exogenous origin. We may have intoxications set up by bacteria kept as household pets in our own intestines, or we may have toxins which develop from the waste of our own tissues under certain conditions. While the anemias are now divided into primary and secondary, he believes the time will come when primary forms will be abolished and all recognized as secondary. Since Dr. Herter's recent paper, he believes that bacteriologists are now on the track of the particular organism causing pernicious anemia.

In regard to the use of iron he believes that large doses in chlorosis often very considerably improve the condition of the blood, but he deplores the indiscriminate use of iron. It was thus reasoned out in the earlier days: There is hemoglobin in the blood; hemoglobin contains iron; therefore, if the blood is low in color, give iron. But the flaw here is, that although hemoglobin contains iron, it can be split into two moieties, one containing all the pigment, the other none, and the latter contains all the iron. Giving iron will not make pigment.

Another point refers to the dose of iron and the way to give it. The total amount of iron in the body is about 45 grains, and we frequently give 20 or 25 grains a day in Blaud's pill, while the actual amount of iron that can be absorbed is only three-quarters of a grain a day. Moreover, more iron than the body actually needs for its maintenance is contained in the ordinary articles of diet unless these be unduly restricted. The trouble lies in a faulty absorption of iron if anywhere. Dr. Hutchinson believes that if we would study our own cases from the point of the toxins and consider the iron administered as having an effect on intestinal sepsis and putrefaction, we would get better results.

DR. JAMES K. KING, Watkins, N. Y., said that in a few of his cases the blood pressure was very low; in one case it was as low as 40. This was very unusual. He recently saw a woman, 52 years old, in whom had been made the diagnosis of pernicious anemia, according to the most exhaustive examinations. The blood picture of pernicious anemia seemed positive. Every therapeutic measure, including hydrotherapy, vibration, massage, electricity, the various forms of iron, tonics, the red iodid of mercury internally, and hypodermics of the salicylate of mercury had been tried without effect. Colon irrigations were also used faithfully with Kemp's tube for cleansing the bowels, relieving toxemia, aiding in the absorption of food, and stimulating the circulation. No improvement resulted from these various measures. It seemed as though nothing more could be done for her relief. A prominent physician was called from New York, who gave little hope of any improvement. The circulation was so bad and the heart action so weak that she suffered much from dyspnea. At this time saline injections were given twice a day after a thorough irrigation, beginning with eight ounces and working up to a pint twice a day. This amount was allowed to remain after the irrigation. These injections raised the blood pressure, as shown by the readings from the instruments, and also from the physical symptoms, such as pressure, headache, etc. It is now two months since the treatment was begun. The blood pressure has risen from 40 to 80 mm. mercury. The blood count increased from erythrocytes, 1,040,000; leucocytes, 2,340; hemoglobin, 20 per cent.; to erythrocytes, 2,381,000; leucocytes, 3,800; hemoglobin, 43 per cent. She has improved very much in every way, and goes about like other people. After trial with all other things with absolutely no effect on the condition, it was a great satisfaction to see these results from the saline injections. The saline fluid should be retained so that it can be absorbed.

DR. ALLEN A. JONES, Buffalo, said that in a series of 8 cases of pernicious anemia that came into his hands since Oct. 1, 1906, in private and consultation practice, one patient was 70 years of age, one 63, another 55, and the rest between 40 and 60, excepting two women whose ages were 33 and 29, respectively. With regard to the blood picture in pernicious anemias, there is the low red cell count, with a change in the color index and the large cell type. Also it is not always easy to find the megaloblasts; he did not think we should rely on the presence of megaloblasts to come to a definite diagnosis of pernicious anemia if other things were present. Before arriving at a positive diagnosis a study of the stomach should be made; in the majority of these cases of pernicious anemia there is found a complete suspension of the secretory function of the stomach, an achylia gastrica. This is so common that Dr. Jones regards it as of considerable value. He spoke of cases, of course, in which he could exclude the secondary

anemias. He depends in iron therapy on the use of the Blaud pill, well prepared, in preference to the proprietary preparations. He feels that he loses valuable time if he places his patients for weeks or for months on the proprietary preparations of iron. If one gets a good Blaud pill he will get decided and good results, not only in cases of typical chlorosis, which are rare, but in many cases of secondary anemia. With regard to the treatment of pernicious anemia, occasionally it was his experience to find a patient improve so decidedly under treatment that he continues well for years. Dr. Jones has under observation a woman in Pennsylvania illustrating this point. It is remarkable how she improved under the use of arsenic. Why, he does not know. All physicians are familiar with the marked improvement that occurs in some cases under the use of arsenic.

Dr. Stanley P. Black, Los Angeles, Cal., discussing Dr. Cabot's paper, said he believes that Dr. Cabot is not justified in separating Class 1 into two groups. There is no question in Dr. Black's mind but that all forms of anemia have a cause, and that there is no such thing as a primary anemia. When called primary anemia it is because of our ignorance or inability to find the cause. So *Bothriocephalus latus* anemia and other forms of anemia of toxic nature should be left in the same class; they have the same blood picture. He thought that ultimately the cause of all the anemias would be found. With regard to the physical signs in chlorosis, there is one sign that is frequently present in these cases, a hypoplasia of the genitalia and cardiovascular system. This is frequently found in chlorosis and is an important factor in the diagnosis. There is another type of blood picture that Dr. Cabot has not mentioned, practically a preliminary picture in secondary anemias, the chlorotic type, in which the hemoglobin is reduced, but the red cells are not reduced to the same limit. After severe hemorrhages there is an immediate reduction in the number of red cells; but the hemoglobin falls *pari passu*, the color index being normal. After a certain length of time, the hemoglobin is diminished and we get the same blood picture as in chlorosis. This type is found very often in secondary anemias before they reach the chlorotic stage.

Dr. Abraham J. Hobson, Hampton, Iowa, said that, as a practitioner in a country town of about 3,000 inhabitants, he has been struck with the frequency of pernicious anemia there. In his practice covering a period of twenty years he saw at least 20 cases, and in none of them was there any doubt as to the diagnosis. A careful examination had been made and the diagnosis was based on the blood findings; some had been diagnosed by specialists in Chicago. He has at present three cases in his own practice and two cases seen in consultation. He asked: "Is pernicious anemia more com-

mon in Iowa than it is elsewhere in this country?" These five patients are all women, the youngest 35, the oldest 65 years old. All are farmer's wives and well to do, and therefore the anemia could not be the result of starvation.

DR. FRANK SMITHIES, Ann Arbor, Mich., said that whatever form of anemia presents itself, an exact diagnosis can only be obtained by study of the complete picture—the clinical manifestations as well as the findings from careful examinations of the blood. With regard to the treatment, he wished to lay special emphasis on rest, fresh air and proper diet. By rest, he meant absolute rest in bed, often for a long time. In particularly severe cases, ice bags over the precordia do much to control dilatation and slow the pulse. By fresh air, he means outdoor air, the patients being in the sunshine eight or ten hours daily. They should be carefully protected from the rays, to guard against sunburn. With regard to diet, he has seen many cases in which careful feeding—sometimes by the spoonful, at short intervals—had carried patients over blood crises, where all forms of medication had accomplished nothing. In ordinary cases he has seen the best results come from a rich albuminous diet, with plenty of raw meat and egg. He was glad to note that a previous speaker had mentioned the importance of stomach analyses in anemics. In pernicious anemia especially, he had found achylia common. In these patients, hydrochloric or tartaric acid should be supplied, and in the cases of low motility, lavage should be given. In reference to the finding of low blood pressure which one of the speakers had mentioned, this is so commonly found in diseases not due to anemia that he did not consider it of diagnostic value. He had used the Erlanger apparatus and found that low systolic and diastolic pressures are the rule, but the findings have but rarely been of great value in directing therapy. He, too, had noted the large number of cases which came to Dr. Dock's clinic from the country-side. He had, however, always considered that this was because of the geographic situation of Ann Arbor, rather than that the disease was especially peculiar to farmers. The disease is rarely recognized in the villages and small towns, and consequently the cases drift into institutions or larger cities. He thought, however, that this point might be worth investigating. Perhaps, then, some definite regions of origin might be discovered.

DR. NORMAN BRIDGE, Los Angeles, Cal., said that he failed to hear mentioned the one medicament of great value in chlorosis. This drug is pre-eminently valuable in chlorosis as a therapeutic measure capable of increasing the hemoglobin of the blood. It has been shown, and clearly enough, he believes, that iron in many of these cases is of little value. The one drug he had in mind was calomel in tonic doses—not cathartic doses—that is, from 1/50 to 1/30 of a grain, given three times

a day, but not oftener. How it works or operates he does not know or pretend to know. But that it has a power vastly greater than the iron preparations in securing good blood and increasing the iron in the blood, there was no question in his mind. It should be given at least a month continuously, and there is, of course, no objection to giving at the same time iron or any better tonic—or all together.

Dr. C. H. Bunting, Charlottesville, Va., referred to the multiplicity of the causes of pernicious anemia. Dr. Cabot has divided this type into pernicious anemia and the anemia due to parasites. Experimental work has shown that one may expect to find a multiplicity of causes, because various toxins can be used to produce the same picture in animals. In human pathology, then, one may have a variety of causes producing the condition in the blood which is described as the picture of pernicious anemia. He believes that the great majority of the cases, however, which are recognized as cases of pernicious anemia are due to practically the same cause; this is true, although clinically and pathologically one can not separate the cases which are due to a parasite from those which are due to unknown causes. As to the treatment, there is one suggestion to be made from the pathologic side: Rest, fresh air and diet are very important in enabling the bone marrow to produce and reproduce new red cells. But the essential thing must be the removal of the cause. In the *Bothriocephalus latus* anemias we have a good example of what results when the cause is removed, recovery. Consequently, he believes that we have one certain indication in every case of pernicious anemia, and that is the careful treatment of the gastrointestinal tract.

Dr. Bailey K. Ashford, Washington, D. C., said that he approved of Dr. Hutchinson's remarks regarding the influence of iron. Iron is of value in certain cases of uncinariasis in which the recovery is slow; in such cases iron does well. But ordinarily iron is not necessary. As to the possibility of uncinarial anemia being produced by a toxin, we have not yet been able to demonstrate any such toxins, but there are certain facts which might make this probable in uncinariasis. He wished to call attention in this connection to the hyaline degeneration of the arteries of the Malpighian corpuscles of the spleen.

Dr. Richard C. Cabot, Boston, said that Dr. Bunting's classification of anemias into primary and secondary is simply a question of convenience; there is the same clinical picture and pathologic anatomy in the anemia from *Bothriocephalus latus* as in pernicious anemia. It is merely convenience that makes us call one primary and the other secondary. Dr. Cabot said that Dr. Ashford's work in Porto Rico is really a campaign against a disease of the whole people, for a considerable majority of the population of Porto Rico

have uncinariasis. Now through the energy and honest effort of Dr. Ashford the island is likely to be freed of the disease. Dr. Cabot said that he never hears or speaks of this disease but that he feels the greatest debt of gratitude to Dr. Ashford for what he has done toward saving the population of this island from inefficiency and from disease. In regard to the existence of pernicious anemia in the rural districts Dr. Cabot said that out of 337 cases he has seen, more than two-thirds come from the rural districts; whether a coincidence or not, this certainly is a striking fact. Pernicious anemia will be found to be a common disease in every part of the country if it is looked for. Pernicious anemia is ten times more common than myxedema and five times more common than leukemia. Dr. Cabot has tried saline injections, as he has tried many other treatments for pernicious anemia. Out of the 337 patients with pernicious anemia three are alive, and he does not believe they got well by reason of what he did for them. This fact made him rather slow in accepting anything in the way of therapeutic measures, whether intestinal flushings, or arsenic, or rest, fresh air, which he always gives, or anything else. He has never been able to make up his mind that arsenic does any good.

Dr. S. J. Meltzer, New York, said that it is not fair to bring up here the fatal case in Philadelphia as an argument against the value of direct transfusion as a method. The case may prove, if it proves anything, that in certain pathologic states transfusion is inadvisable. Crile, however, introduced the method of direct transfusion primarily for anemias caused by hemorrhages of traumatic origin. In these cases the direct transfusion apparently renders excellent service. The method, therefore, marks a distinct progress in the treatment of anemia, and that is all Dr. Meltzer claimed for it. The celebrated clinician, Niemeyer, is quoted as saying that his success was due to the use of iron in chlorosis. He gave Blaud's pills in large quantities. Dr. Meltzer would advise other physicians to do the same, the opinion of some physiologic chemists and hematologists notwithstanding. The history of the pharmacology of iron for the last twenty-five years teaches that, in the practice of medicine, the clear-sighted clinician is very frequently a safer guide for the practitioner than physiologic chemists, some of whom venture to offer positive opinions in fields in which they possess neither theoretical nor practical personal experience.

THE PROPHYLAXIS AND GENERAL MANAGEMENT OF ACUTE RHEUMATIC FEVER.

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PHILADELPHIA.

Prophylaxis depends on etiology and pathology; while general management must be co-ordinated with specific treatment, and modified to meet any complications that may arise. It is impossible, therefore, to discuss these two topics without some reference to the subjects that have been assigned to other speakers. Such reference will, however, be chiefly in the way of brief allusion, taking for granted the facts that have been, or will be, elaborated by my colleagues in the symposium.

A. PROPHYLAXIS.

The prophylaxis of acute articular rheumatism has four phases. These refer, respectively, to (1) the initial attack; (2) the complications, especially the cardiac affections; (3) relapses; (4) recurrences. At present this prophylaxis is, in all its phases, largely empirical, because pathology and etiology have not yet given us the necessary exact bases for an exact scientific preventive régime.

We are all agreed that the condition called acute articular rheumatism is a special form of multiple arthritis and that it is an infection. Beyond that, however, we have no certain knowledge regarding its etiology. Acute rheumatic fever, otherwise known as acute rheumatic polyarthritis, is an infection, but the infective or-

ganism, if there be but one, has not been demonstrated beyond doubt.

I am inclined to the view that there is a group of organisms, possibly cocci, any one of which under certain conditions may give rise to acute polyarthritis. I do not refer here to those organisms which we have in mind when we speak of gonorrheal arthritis, scarlatinal arthritis, diphtheric arthritis, etc. These are specific microbes, giving rise incidentally, as it were, to specific forms of acute polyarthritis, not properly to be termed rheumatism. But I intend to express the opinion that febrile and articular phenomena essentially the same—that is to say, showing only such individual differences as are ordinarily encountered even among patients infected with a single definite specific germ—may arise from the individual or combined action of a number of germs, probably closely related and possibly allied to the organisms of scarlatina and of erysipelas, and that to this association of phenomena the old name "acute articular rheumatism" may be applied for the present.

It is not beyond the bounds of possibility—rather is it extremely probable—that among these organisms are those which ordinarily inhabit harmlessly the mouth, the nose and the throat. Certain it is that the tonsils and other faucial and buccal—even gingival—structures frequently show the first signs of the infection which is afterward expressed by joint phenomena, cardiac phenomena, etc. Also, it is well known that cold and exposure aid in precipitating the general train of phenomena. Furthermore, experience warrants the assertion that only certain individuals out of the entire number of those exposed both to cold and to the specific germ, or group of germs, manifest the association of symptoms constituting acute articular rheumatism. Therefore, it seems to be highly plausible that these individuals possess a certain susceptibility, for which as yet we have no better designation than the time-honored (or dishonored) term, diathesis.

Of the nature of that diathesis—whether it is chemical or physical, morphologic or dynamic, whether it has a distinct anatomic location, or affects the fluids and tissues of the body generally—we are not in position to speak definitely. Certainly it has an intimate relation with nervous function and especially with the vasomotor apparatus, perhaps also with the tissues of the organs of circulation; certainly, too, it modifies decidedly the chemistry of the blood, the urine, the sweat—perhaps all fluids.

These considerations determine the first phase of prophylaxis, namely, that which is directed against the initial attack. But this can well be discussed together with the prophylaxis of recurrence, and further remarks may be postponed until that subject is taken up.

PREVENTION OF COMPLICATIONS AND RELAPSES.

The second phase of prophylaxis relates to the complications and especially to the cardiac complications. This may seem an undue extension of the term prophylaxis. If so, let us consider the matter under the head of "general management." The most important point in the general management of a case of acute articular rheumatism, then, is the prophylaxis of the complications and especially of the dangerous cardiac complications.

REST, ALL IMPORTANT.

The prevention of relapses and of cardiac complications is practically the same. It consists of several divisions. The first is rest. The second is rest. The third is rest. And the fourth, fifth, sixth, seventh and *ad infinitum*—rest. This can not be emphasized too strongly. And by rest, I mean Rest. Nothing half-willed or half-hearted; no half-way timid compromising; no cowardly abbreviation; but Rest. Enough rest; rest long enough; rest rigid enough; rest, physical and mental; rest, cardiac, muscular, articular; complete rest. The great majority of the chronic cardiac lesions which

follow acute articular rheumatism are beyond question due to the neglect of rest. It is rather a misfortune for a man to have what is ordinarily termed a "light attack" of rheumatism, for the joint phenomena to disappear too soon, or for the heart to have remained apparently strong and unaffected during the attacks. It is one of the hardest things in the world for the physician to enforce rest under such circumstances; for it is almost hopeless to make the patient understand the necessity of keeping his bed when he feels so well. Unfortunately the physician himself may fail to realize the importance of rest, as I have frequently observed in consultation and in hospital wards.

Shall the rest be prolonged for six weeks—which is the minimum—or shall it be nine weeks or twelve weeks? I do not know. It depends on the case. The patient must rest until all danger of cardiac complication, all danger of straining the weakened and infiltrated heart muscle by full use too soon after recovery (for it is the muscle rather than the valves to which we must look most carefully), all danger of relapse from imprudence has passed away.

When, notwithstanding the skilled administration of salicylates, pain tends to make the patient restless fixation of the joints, local analgesic applications, even the administration of bromids, or codein, or morphin, may be indicated, apart from all other considerations, as measures conducive to rest.

Convalescence must be skillfully managed; the patient is first to sit up in bed a little while, then a little while longer, then out of bed a little and a little longer, and very gradually, and only very gradually, allowed to resume full activity. This is the true prophylaxis—difficult to enforce, but necessary and usually effective.

AUXILIARY MEASURES TO PREVENT COMPLICATIONS.

In addition, there are certain more direct therapeutic measures warranted by experience, and for which I have

as yet no satisfactory explanation, which may be adopted to prevent cardiac complications. One is the precordial blister. The blister need not be over the precordium, however; it may be above—say in the second interspace to the left of the median line, covering a space of one square inch and leaving the precordium free for examination. As the blister heals, another may be made near it, and the process may be repeated from time to time. That the blister empirically helps to prevent cardiac complications or helps to cut short the course of an existing pericarditis or endocarditis, or pancarditis, or aortitis I have not the slightest doubt. This opinion rests in part on reading—i. e., on the reports of men of good judgment and large experience; in my part on my own careful observations, extending now over fully twenty-five years; for I first saw the method applied during my undergraduate days in my brother's service in the German Hospital of Philadelphia. The scientific explanation is in the future. The empirical fact is here to be accepted.

ALKALINES AND IRON.

Another useful measure is the administration of alkalines. Whatever the abnormal chemism may prove to be in detail, the acid condition of the body fluids as shown by the acid sweats, by the acid saliva, by the heightened acidity of the urine, gives us a sort of chemicopathologic indication for this measure and empirically it is extremely useful. Alkalines must be administered promptly and sufficiently; they must be so administered as to make the urine alkaline as soon as possible and to maintain its alkalinity throughout the attack. The use of salicylic agents, together with alkalines, is not counterindicated, and, in fact, I usually employ them together. With anemic patients, with old patients, with patients who have had many previous attacks, the alkaline treatment, however, is usually inadvisable. In such cases tincture of the chlorid of iron, as recommended by British observers many years ago, is the best remedy now

at our command. It is to be given fearlessly. The dose is *enough;* it is to be repeated sufficiently often, and to be continued so long as necessary. Individualism being necessary, I can not give any exact figures. I frequently prescribe from 20 to 30 minims, sufficiently diluted, every second hour. Ferric medication and salicylic medication can be associated. I am in the habit of prescribing the mixture which I introduced about 22 years ago under the name of "mistura ferro-salicylata" and in which a simple pharmaceutical expedient is employed to prevent the precipitation of ferric salicylate.[1]

PREVENTION OF RECURRENCES AND OF INITIAL ATTACKS.

The prevention of recurrences and of initial attacks in those in whom we have reason to suspect from their family history or personal peculiarities the existence of that which, for lack of a better term, we designate the rheumatic diathesis, has several phases, each of considerable importance.

CARE OF MOUTH, NOSE AND THROAT.

Scrupulous attention must be given to the condition of the mouth, the nose and the throat. This includes regulation of diet; cleansing of the stomach and bowels; attention to the tongue and teeth; treatment of nasal catarrh, if present; destruction of the tonsils, if necessary; removal of adenoid growths and of postlingual glands; and, in general, whatever is needed to keep the alimentary and respiratory mucous membranes clean and healthy, and to get rid of any residual focus of infection. It is not necessary to go into details.

THE AVOIDANCE OF EXPOSURE.

The subject of exposure may be treated briefly. While the popular apprehension of "drafts" is in many aspects

1. The revised formula follows: Sodium salicylate (true), 1 dram; tincture of ferric chlorocitrate, 1 fluidram; glycerol, 1 fluidram; gaultheria water, sufficient to make 1 fluidounce. Mix. Dose: 1 to 2 fluidrams in water every hour to every fourth hour. Sodium bicarbonate, not exceeding 60 grains to the ounce, may be added, if desired, and with slight occasional shaking the mixture will remain clear.

ludicrous, yet it is not wholly without foundation in fact. Benjamin Franklin's experiments on himself are conclusive as to this. Unequal heating or unequal chilling—as when, for example, a person sits with one side of the body turned to an open window in an overheated room—produces local disturbances in the circulation and innervation which may either afford a *locus minoris resistentiæ* for bacteria or toxins or may, through perversion of local metabolism or through stagnation of the products of normal waste, give rise autogenetically to morbid changes. A patient who is convalescing from acute rheumatism, therefore, needs to be protected from local chilling, even of slightest degree. This does not mean that fresh air is to be excluded from the sick-room, but it does mean the avoidance of drafts, the screening of the bed if necessary and the proper disposition of clothing and bedcovering. Beyond this is the avoidance of exposure in the more ordinary sense; exposure, that is, to an extreme degree of cold or to dampness with or without extreme cold, and independently of the unequal incidence of cold or dampness on different parts of the body. Those who have seen cases of paroxysmal hemoglobinuria, of Raynaud's disease, of ordinary chilblains and frost bite, or even of the various degrees of cyanosis of exposed extremities produced by cold, need no further evidence either of the morbific effects of low temperature or of the manner in which susceptibility and reactive power vary in different individuals. As in the nearly comparable case of lobar pneumonia, the circulatory changes brought about by exposure assist in determining the pathogenic activity of the infective organism or organisms; the difference being that, so far as yet appears, there is no definite personal or constitutional liability to pneumonia, as there is to acute articular rheumatism. Exposure, therefore, to a mild degree of cold affecting different portions of the body surface in a markedly unequal manner, or to a high degree of cold acting equally on

uncovered surfaces or on the body in general, tends, especially if combined with dampness, to determine, in susceptible individuals, relapses or initial attacks and must be avoided.

EDUCATION OF THE VASOMOTOR REACTION.

As, however, exposure of one or another kind is among the unavoidable accidents or incidents of life, it is highly important to bring the patient, if possible, into condition to withstand at least its ordinary degrees. To this end, the resistance of the vasomotor system in especial, is to be strengthened by appropriate physiologic exercise.

In our consideration of the etiologic moment of cold and dampness, I purposely included those extreme types of vasomotor changes described by Raynaud and those very common instances which every one sees daily during the winter, to emphasize three facts: 1. The circulatory failures caused by low temperature vary greatly in individuals of different constitution. 2. In certain phases of this variation they afford opportunity for the pathogenic action of micro-organisms and toxins. 3. Some of the abnormal phenomena observed in and around joints during an attack of acute articular rheumatism are not inflammatory in the true sense, but indications of vasomotor paralysis. There is a vicious circle, or rather, a vicious network, in which local stagnation from cold, the production of autogenous and microbian toxins, further vasomotor paralysis due to intoxication, augmented production of toxins and associated inflammation, act and react on one another. The liability to the initiation of these changes may be reduced by systematic measures designed to educate and exercise the vasomotor reaction. Several of the methods of physiologic therapeutics are available for such exercises, the most useful being (1) massage, (2) electric-light baths and (3) thermic stimulation by means of hot and cold water.

1. *Massage.*—It is not necessary to go into detail, but a few general hints may be given. As a rule, the best form of application is general massage, a systematic manipulation of one part of the body after the other, as followed in the practice of Weir Mitchell.[2] In this, as in all other forms of treatment, however, skilful modifications suited to the spinal conditions presented by the individual patient are required. Control over the vasomotor reflexes may also be established by that special form of massage to which the names of "manual therapy," "mechanoneural therapy" and "cheiropraxy" have been variously applied. It consists of intermittent pressure by the finger tips along the vertebral column, the interruptions being frequent or slow according to the effect desired or produced. Vibratory mechanical apparatus may also be used. In my judgment, however, general massage is far superior to any other method.

2. *Electric Light.*—The incandescent electric-light bath may be employed locally or generally. When used simply to educate the vasomotor reactions it is best to use red light and to limit the application to 10 minutes or less, following it by a brisk rub with cold water and friction with a rough towel or glove.

3. *Hydrotherapy.*—Various hydrotherapeutic measures are applicable, chiefly those in which hot water and cold water are applied alternately. Here, too, strict individualization is necessary. Temperature, pressure and duration must be prescribed as definitely as the components of a pharmaceutical mixture. Douches, affusions, general baths and local baths may be employed. Vigorous friction should always accompany the use of cold water in any form and the application should be brief; chilling is always to be avoided, and the success of the treatment depends on the promptness and completeness of the reaction following the cold application. A simple measure, which patients may

2. Solis-Cohen's System of Physiologic Therapeutics, vol. vii, pp. 25 seq.

easily employ at home, is first to sponge the body with water at a temperature of from 104° to 108° F. This procedure should not occupy more than three minutes. Then, taking in the hand water at a temperature of from 70° to 60° F., the body is to be rubbed vigorously therewith. This procedure must not occupy more than two or three minutes and is to be followed by a vigorous drying rub with a rough towel or glove. The best time for this application is on rising in the morning. No other apparatus is required that two basins—one for the hot water and the other for the cold water—and a thermometer. Even the thermometer is not indispensable in this particular form of application, as the sensations of the patient are a fair guide to the permissible temperatures of the hot and cold water. It is sometimes necessary to begin in a gentle and gradual way by limiting the cold application to a portion of the body. Thus at first only one forearm may be rubbed with cold water, then both forearms, then both arms and the upper part of the chest and so on, extending the area gradually and symmetrically until the whole body is involved. When the patient enjoys possession or use of a modern bathroom, a brief plunge in the hot water may be followed by a cold rub or cold shower; or we may employ alternate hot showers and cold showers, or a hot shower followed by a cold rub, or any other modification that suits the fancy or necessity of the patient. The important matter is to remember that the treatment must be gentle and brief, that friction must accompany the cold application however made, and that the sufficiency of the reaction is the test of the efficacy of the application.

ELIMINATION.

Regular and sufficient elimination is a necessary prophylactic measure. The urine must be carefully examined from time to time not only as to its acidity and the presence of such abnormal constituents as albumin,

casts and excessive oxalates and urates, but also as to its general nitrogenous and ammonia content, the presence or absence of ethereal sulphates and their proportion to the fixed sulphates and, in general, whatever will throw light on the general metabolic balance. Apart from this an occasional therapeutic sweat once a month or oftener, according to the individual case, is highly desirable. The incandescent electric-light bath may be employed for this purpose, in which case the white light is to be used and the duration may be twenty minutes or longer. The hot-air cabinet and the Turkish bath, the dry hot pack or any other available means not specially counterindicated by the general condition or cardiac lesions of the individual patient, may be employed in the absence of facilities for the electric-light application, which, however, is to be preferred over all others when available. A convenient and cheap apparatus for home use is being made at my suggestion and will soon be procurable at the shops. A cold coil or cold compress should be placed over the head and another over the precordium, during the application of heat. Perspiration should be allowed to continue for from thirty minutes to one hour, after which the patient should receive an alcohol rub, to be followed by friction with cold water or by general massage. If massage be employed, there should be, as in other instances of its employment, complete rest for at least an hour following.

DIET.

An important feature of prophylaxis is the regulation of diet. The food should be simple and nutritious and should be so chosen as to yield a minimum of nitrogenous waste. In addition, the carbohydrates should be cut down to the lowest point consistent with the maintenance of nutrition, and oil and fats substituted, so far as possible. This is not only to avoid fermentative processes in the gastroenteric tract and their undesirable consequences on the body fluids in general, but also

because patients of the rheumatic diathesis exhibit a distinct failure in carbohydrate metabolism. While thus restricting the diet, it is a mistake, however, to be too rigid. Red meat should be allowed once daily, an occasional baked potato is to be advised, and well-cooked rice is to be permitted at any time. In general, milk and milk products, cereals, fruits, nuts and green vegetables should form the principal portion of the diet. Pork, veal, crab, lobster and other crustaceans, hashes and messes of all kinds are to be avoided, as are likewise pickles, sweets and pastry. As in all other matters, however, the diet is to be individualized; with an extra restriction here and a greater liberty there. Water should be taken freely. In the ordinary case mineral waters have no advantage over pure, clear hydrogen monoxid, but in cases with persistent pain and stiffness mild alkaline waters—for the obese, sulphur waters, and for the anemic, aged and feeble, alkaline chalybeate waters—are useful.

B. GENERAL MANAGEMENT.

Much of the general management of the attack has been covered in discussing the prophylaxis of the complications, relapses and recurrences. The most important measure is rest. This I would again emphasize. The diet should be exclusively milk for at least two weeks and longer if necessary; that is to say, during the entire duration of febrile temperature or joint involvement. If necessary, the milk may be pancreatized or diluted with Vichy water. Increase of diet is to be gradual and no flesh food is to be given until convalescence is fully established, which means for at least six weeks after the beginning of the attack. As a matter of course, the bowels are to be kept freely open; calomel at the beginning, followed by an alkaline laxative, is the usual and probably the best method. During the further course of the attack, alkaline laxatives are preferred. The importance of keeping the urine alkaline has already been mentioned, and with this goes, of course, the

necessity of keeping up the quantity of urine not only to, but beyond, the normal point. Water is the best diuretic. In some cases, especially when pathologic sweating is excessive, a therapeutic sweat, which may readily be given by means of an incandescent electric bulb introduced beneath the bed covers supported on a cradle, is highly useful.

MANAGEMENT OF CARDIAC COMPLICATIONS.

Reference has been made to the prevention of cardiac complications, and but a word further need be said as to their treatment. The blister is useful, alkalines should be continued. Whether or not to continue the salicylates is an open question, and the general condition of the individual patient must determine it. If articular manifestations continue to be severe, it is usually best to keep up the salicylic treatment. Otherwise, in the actual presence of endocarditis, or pericarditis, it is better to discontinue that drug. Iron is sometimes of service, and I have on several occasions during the last few years resorted to the administration of colloidal silver by the mouth or rectum, or in very severe cases even by a vein. In am convinced that in many cases it is extremely useful, though I can not assert that it is always effective. Like many other useful remedies, it suffers discredit from extravagant and unwarranted laudation. When etiologic data become more exact our use of remedies can be more discriminative. The rectal dose of the silver preparation is from one-half to one ounce of a 5 per cent. solution, twice daily, or oftener if necessary, provided the bowel is tolerant. By the mouth a teaspoonful of the same solution may be given every two or three hours. By the vein from 30 to 90 minims (2 to 6 c.c.) of a 3 per cent. solution or of 5 per cent. solution, if it can be made sufficiently fluid, may be given in one or two or three or more times in the twenty-four hours, according to the urgency of the case and the difficulty or ease of administration.

Ammonium bromid and strontium bromid are sometimes useful in the treatment of pericarditis, especially if there be great restlessness; if necessary, opium should be administered in sufficient quantity to control pain. I prefer codein to other derivatives of opium. A precordial coil is extremely useful. When first applied, water of about 90° F. should be run through it for two or three minutes; after this, ice water. The coil may be kept in position continuously or removed and reapplied from time to time, according to the effect on the pulse and on the general comfort of the patient. In the absence of the precordial coil, an ice bag is a clumsy, but not inefficacious substitute.

LOCAL APPLICATIONS TO JOINTS.

Local applications to the joints are many, and, while most of them are useful in nearly all cases, sometimes patients exhibit idiosyncrasies which must be regarded. Among the preparations which I have found most generally applicable are ichthyol, methyl salicylate, sodium bicarbonate with tincture of opium in the well-known "Fuller's lotion," "lead water and laudanum" and a saturated solution of magnesium sulphate, as suggested by Dr. Tucker in surgical arthritis. Sometimes it is best to wrap the joints in cotton or lamb's wool, dry. Sometimes it is well to cover the local application with oiled paper or oiled silk and sometimes it is best to permit evaporation. There is no invariable rule. One must be guided by the general condition and the special requirements of the individual patient. When there is a tendency to persistence of effusion around the joint after febrile movement has subsided, I have found it useful to apply two or more very small blisters an inch or so beyond the margin of the effusion. When the effusion is obstinate, it is well to encircle the limb with, say, half a dozen of these small blisters, each about half an inch in diameter.

CONCLUSION.

In conclusion, I wish to leave with the Sections two words as guiding principles in the management of all cases of articular rheumatism: First, and above all, for every patient, *rest,* strict enough and long enough. Second, as to each case, and in regard to the measures auxiliary to rest—whether specific medication, alkalinization, diet, or the use of purgatives or diuretics, of iron, of blisters, of precordial coils or ice bags, of local applications to the joints, or of any other of the prophylactic or remedial means to which allusion has been made—strict individualization. But once more let me say that the measure of supreme importance in every case is *rest.*

THE TREATMENT OF RHEUMATISM BY SPECIFICS.

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I was asked to discuss the specific treatment of acute articular rheumatism or that kind of treatment which is supposed to combat the cause or neutralize the toxins of the disease.

Unless we know the cause of a disease, and are convinced that a certain remedy destroys that cause or neutralizes it, we can not call a remedy a specific. Therapeutists, however, were certain that mercury was a specific for syphilis and quinin for malaria before all this information had been obtained in regard to these diseases. As yet we have not the requisite knowledge of the cause of rheumatism which would enable us to say with positiveness that there is a specific for the disease, although the salicylates possess many of the attributes of one.

Almost from the time that rheumatism was clearly recognized its cause has been believed to be a noxious foreign agent in the blood and fluids of the body, and at first this was thought to be autogenous. Many clinicians confusing its pathology with that of gout, suspected uric acid to be its cause, and later professional opinion ascribed the same rôle to lactic acid. Comparatively recently, however, physicians have become convinced that acute articular rheumatism is an infection and of microbic origin.

Naturally, therapeutic views have changed with these changing concepts of the nature of the disease. At-

tempts were made to eliminate the harmful matter by bleeding, by purgation, by emesis and by diaphoresis. Such was the treatment of rheumatism until toward the middle of the last century, when it was widely believed that the disease was due to an acid in the blood and probably to lactic acid. Therefore, alkalies were given as an antidote. It is true that many years before alkalies were prescribed empirically for rheumatism, but at this time they were used as a specific to neutralize the supposed cause of the disease.

Although the alkaline treatment of rheumatism can no longer be regarded as specific, it deserves consideration, for it is used to-day, partly because the feeling still prevails in the profession that it is advantageous to neutralize some acid in the blood, and still more because statistics make it probable that the alkaline treatment averts endocardial inflammation.

It has been definitely proved, however, that lactic acid, which by Richardson and others was believed to be the cause of rheumatism, is not its cause. Moreover the reduction in alkalinity of the blood in this disease is not greater than in many other fevers and other pathologic states; therefore, the acid theory has no adequate foundation. The claims of Furnivall, Chambers, Dickinson and many others that endocarditis is less liable to occur and that the disease is less prolonged when alkalies are given freely can not be dismissed summarily. On the contrary, averaging the statistics of several of these writers, it appears that cardiac complications arise in only one case in thirty under alkaline treatment and in one case in four under other kinds.

The drugs used to increase the alkalinity of the blood are chiefly the potassium and sodium bicarbonates, citrates and acetates. To make them efficient, enough must be given promptly to render the urine strongly alkaline, and it must be kept so. It usually requires from 1 to 1.5 grams of these drugs administered at intervals of from three to four hours to accomplish this re-

sult. The manner in which they lessen the liability of those suffering from rheumatism to endocarditis can not be explained.

Although it must be admitted that the alkaline treatment of acute articular rheumatism is useful, it is in no sense a specific.

In 1874 Maclagan advised the use of salicin as a specific in acute articular rheumatism. Soon thereafter salicylic acid was shown to have similar powers and it was proved that salicin contains salicylic acid and depends on it for its effects in rheumatism. Because of the tendency of salicylic acid to irritate the stomach, sodium salicylate was soon substituted for it, and for a quarter of a century this drug has held its place as the best remedy for acute articular rheumatism. If any remedial agent deserves to be called a specific for rheumatism this does.

Unfortunately the physiologic action of this commonly-used drug has never been demonstrated so thoroughly as it should be. In therapeutic doses it has little or no effect on the cardiovascular system. Sometimes it causes a temporary rise in arterial tension but oftener it produces no effect. In very large doses it weakens the heart and lowers arterial pressure. In toxic doses these effects are pronounced.

It does not affect healthy sensory and motor nerves nor the central nervous system unless toxic doses are given; but in many painful disorders it is a prompt and effective analgesic. In large doses it produces the symptome of cinchonism, and in still larger ones or in individuals who are particularly susceptible to it, partial or complete, deafness or blindness, headache, delirium, rapid and deep respiration, even distressing dyspnea, cardiovascular weakness, profuse sweating, maculæ or ecchymoses in skin and mucous membranes, and albuminuria because of nephritis. In fatal cases death may be preceded by convulsions.

Salicylates ordinarily have no effect on temperature in

health, although sometimes very large doses may lower it slightly. This, however, is not a uniform effect. In fever, on the other hand, it is a trustworthy antipyretic. Usually a few minutes after its administration sweating is provoked and almost simultaneously the temperature falls, remaining depressed in moderate cases for from four to six hours, and the pulse rate becomes slower in proportion as the temperature falls.

The drug doubtless circulates in the blood as a salicylate, but it is not certain in what combination.

It is eliminated chiefly by the kidneys, though partly by the liver. Very large doses irritate the kidneys and even excite inflammation of them. Under its influence urea is eliminated in larger amounts, which may be because it stimulates the liver.

Salicylic acid irritates the stomach and intestines, often causing lack of appetite, nausea, vomiting and diarrhea. The salicylate of sodium is much less liable to produce these results, although its mawkish, sweet taste is nauseating to many people.

These physiologic effects of the salicylates do not explain fully the influence of the drug in acute articular rheumatism. In this disease we have to do with fever, and inflammation in one or more joints which causes in them pain, swelling and often slight redness of the skin; there is also sweating, progressive anemia, often inflammation of the endocardium and pericardium and sometimes of the pleura and iris. A few hours after full therapeutic doses of the drug have been administered the pain is greatly lessened, the redness of the skin disappears, the swelling subsides and the fever abates, although it does not usually disappear entirely until several days after the affected joints have ceased to show signs of inflammation. Sweating, which is a phenomenon of the disease, is aggravated. It is also probable that the drug, if administered for many days in full doses, increases slightly the anemia which the disease produces. In the average case pain and arthritis are

controlled by the end of the third or fourth day or sooner. In as many more days the fever disappears so that convalescence may be well established in two weeks. In severe cases a longer time is required to effect these results and various joints may be successively involved before the disease abates. That the course of the disease is shortened by the salicylates is the belief of most physicians.

It is evident that an antipyretic is not all that is needed to produce such marked amelioration as all physicians have seen effected by the salicylates in acute rheumatism, for quinin will lessen temperature as efficiently but does not produce the other therapeutic effects of the salicylates. Moreover, in other fevers the salicylates do not shorten their course or produce the profound general effect on them which these drugs do on rheumatism.

Nor are these results due largely or chiefly to the analgesic effects of the salicylates, for other analgesics act as efficiently but do not produce so specific an effect on rheumatism, although in this they approach nearest the salicylates. Soporifics, such as opiates, lessen the pain of rheumatism but do not lessen the joint swelling or fever or shorten the course of the disease.

The most noticeable specific effect of the salicylates, however, is the prompt disappearance of the redness, swelling, tenderness and pain in and about the affected joints, for other forms of arthritis, such as gonorrheal or septic arthritis, do not resolve promptly even when the salicylates are given in the largest therapeutic doses.

Moreover, rheumatic inflammation of the eye disappears readily when the salicylates are administered as it does not when other drugs are used.

Although because of these peculiar striking therapeutic effects the salicylates are employed and relied on as specifics for acute articular rheumatism, it is generally admitted by clinicians that they do not lessen the liability of the heart to be affected, a fact which it is difficult to

explain. It has been suggested that they so promptly lessen or relieve the arthritis that the average patient does not keep quiet so long as he should to save his heart. This, however, is not an adequate explanation. If the endocardial and pericardial inflammations were truly rheumatic we would expect them to respond as readily as the joints or eye.

Many patients can not tolerate the taste of salicylic acid or the salicylate of sodium. In a smaller number of individuals these drugs produce nausea, vomiting and often diarrhea and, therefore, can not be used. A few persons possess an idiosyncrasy which makes the salicylates particularly poisonous; in these cases they produce dimness of vision or temporary blindness or deafness, or excessive noise in the ears and headache or delirium. It is very seldom that faintness and great cardiovascular weakness are seen as a result of taking therapeutic doses. In a majority of cases of rheumatism some ringing of the ears and deafness must be produced by the drugs to obtain therapeutic results. Fortunately the other untoward effects are so rare that they do not deter physicians from using these remedies.

Sodium, ammonium, lithium or methyl salicylate, salol, salophen, aspirin and salicin all derive their efficiency from the same active principal, salicylic acid. Because of its irritation of the gastrointestinal canal, however, salicylic acid uncombined is rarely used today. Salol and salophen are only useful in mild cases, for they can not be given safely in sufficiently large doses to control severer ones. Aspirin (acetyl-salicylic acid) in fifteen or twenty-grain doses is efficient in the average case of rheumatism. By many it is thought to be less liable to disturb the stomach than the salicylates; however, I have seen it provoke vomiting so often that I feel little more security in giving it. Oil of wintergreen is efficient, but in large doses it often irritates the stomach and bowels and, therefore, is chiefly used in mild cases and when the height of a severe attack is

passed. The salicylate of sodium is the most reliable preparation. I am convinced also that the salicylate of sodium made from oil of wintergreen is best tolerated by the stomach.

All these preparations are most agreeably administered in capsules. Half a gram of the salicylate of sodium can be given in this way and two capsules will make an average dose. If given thus, care must be taken that water is drunk in sufficient quantities to insure the prompt solution and dilution of the drug in the stomach. A charged solution of bicarbonate of sodium or effervescing sodium or potassium citrate may be drunk instead of water and the alkaline treatment may thus be combined with the salicylates.

Although quinin is a specific in malaria, there are other effective drugs which may be substituted for it. This is true also of the salicylates in rheumatism. Antipyrin is a good substitute, but from a considerable ex- of patients and that convalescence is apt to be more perience with it I am sure that it deepens the anemia prolonged.

If acetanilid and phenacetin are given in quantities sufficiently large to control pain, lessen fever and arthritis they must be administered in maximum or more than maximum doses. They also will deepen the anemia produced by the disease, therefore make convalesence slower and not infrequently produce dangerous symptoms. Consequently they are only adapted to the treatment of very mild cases of short duration.

Clinicians have been convinced that acute articular rheumatism is an infectious disease, but no one microorganism has been identified as its cause.

Menzes in 1902 described a streptococcus which he found with great uniformity on the tonsils of those suffering from rheumatism. From these organisms he prepared a serum by a method similar to that used in making diphtheria antitoxin. When this was injected beneath the skin of patients with acute rheumatism a

reaction was produced, characterized by increased temperature, pain and swelling. But a similar reaction was not obtained by the use of other antistreptococcic serums.

Following the reaction produced by Menzes' serum the pain and swelling in the joints subsided so that in average cases the joints were useful in three or four days and the fever disappeared in six or seven. When the serum was used in chronic cases the symptoms were made temporarily more acute and then improved as in the acute cases. Menzes believes that the cardiac phenomena of rheumatism are also favorably influenced by his serum.

Current medical literature contains few records of experiments with Menzes' serum. Schmidt used it fifteen times, and six of his patients were certainly improved, four subjectively so, and five were not helped. Schaefer obtained good results in six cases.

I believe that this serum has not been used in America, but in 1903 George H. Sherman of Detroit printed the results of his experience during the preceding year with antistreptococcous serum in rheumatism, and in 1906 he published a second paper on the same subject. He found that when injections were begun on the first or second day of the disease recovery usually was effected in a few days. However, if injections were begun much later the course of the disease was not so much shortened. In the cases which he has described in detail the patients began to improve by the fourth day or sooner. They did not exhibit a reaction after the injections as did Menzes' patients. It is noteworthy that in twenty-four of Sherman's cases only two patients developed endocarditis.

Sherman admits ignorance of the organism which causes rheumatism, but points to the fact that a majority of investigators who believe that they have succeeded in findings it, isolated a coccus resembling the streptococcus. He hopes that the antistreptococcus serum of

commerce will produce some good effect, as it often does in scarlet fever.

It is evident that the serum treatment is in a most elementary experimental stage and, moreover, that bacteriologists generally have not been impressed with the rationale of it; therefore, they have not repeated Menzes' or Sherman's experiments extensively.

DISCUSSION

ON THE SYMPOSIUM ON RHEUMATISM.

DR. JAMES M. ANDERS, Philadelphia, agreed that the weight of testimony is in favor of the microbic origin of rheumatism. In addition to the arguments in support of this view, expressed by Dr. Cohen and others, he added that the occurrence of house series of cases, of epidemics and more especially the clinical behavior, including the nature of the commoner complications of acute rheumatism are strikingly confirmatory, but, as is the opinion of other observers, the specific organism has not yet been isolated. Among the predisposing conditions favoring the development of acute rheumatism, he thought reference might have been made to certain morbid conditions of the alimentary canal, because they often precede acute articular rheumatism. The condition known as intestinal autointoxication, however, is the commonest. Dr. Anders regards the diagnosis of acute rheumatism as being exceedingly difficult. In intestinal autointoxication there often develop arthritides which very closely resemble ordinary acute articular rheumatism and Dr. Anders knows of no way in which they can be clearly and definitely separated clinically from that condition. Dr. Anders expressed the opinion that acute endocarditis is the most frequent complication of acute articular rheumatism. In this connection two facts should be borne in mind: First, that in many of these cases the symptoms pointing to acute articular rheumatism are so exceedingly mild as to defy detection, yet latently these conditions may lead to sclerosis of the valves or chronic endocarditis. On the other hand, the influence of age on the liability to rheumatic cardiac complications of rheumatism is quite pronounced and Dr. Anders thought that the profession, in general, does not appreciate the fact. The statistncs of Babinski have always been convincing to Dr. Anders. Babinski found in all but seven cases of a total of 76 instances of acute articular rheumatism, evidences of lively irritation or actual inflammation within the heart. Dr. Anders said that while the period of greatest liability to rheumatic endocarditis and other forms of cardiac complications is childhood, during adolescence, and more especially after the twentieth year, this liability rapidly decreases. A very practical lesson should be

drawn from this fact, namely, that when chronic endocarditis occurs in the middle period of life in a person who has had acute articular rheumatism, but after the twentieth year of age, the likelihood is that the cause of that chronic endocarditis is something else than the preceding attack of rheumatism. As a rule, careful investigation of these cases discloses other and more potent causes for the chronic endocarditis than antecedent rheumatic attacks. Myocarditis, as a complication of acute articular rheumatism, in Dr. Anders' experience, is usually associated with endocarditis, but he is quite certain that he has observed instances of pure myocarditis as a complication of acute articular rheumatism. In his experience pure myocarditis, as a complication, is most apt to arise in case of rheumatism occurring at an unusually late period of life, or, in other words, at a time when acute endocarditis as a complication is becoming less common. As to the treatment of acute articular rheumatism, Dr. Anders thought the time ripe to emphasize the specific action of the compounds of salicylic acid in the treatment of this disease. While a few cases must resist the ordinary measures of treatment, there may be a sufficient accumulation of fluid in the articulations to justify aspiration, Dr. Anders is sure that in the vast majority this surgical procedure must be regarded as contraindicated. He believes that the compound of salicylic acid should be given in sufficient dosage to cause slight toxic effects; as a rule 120 grains of sodium salicylate, per diem, suffices, but in a strong, robust person it may require 180 or more to accomplish this effect.

DR. ALFRED STENGEL, Philadelphia, emphasized several points. First, that in the present state of our knowledge we must regard the acid theory of causation as absolutely exploded, and yet one hears frequent references to uric acid as the cause of rheumatism. Second, and of great importance, is the matter of individual predisposition. This is seen in the tendency to recurrences in rheumatism in certain individuals, as well as in the family liability to the disease. But with regard to recurrence Dr. Stengel thought there is another operative cause which is not considered frequently enough. There is in many of these cases a cardiac lesion, developed in the first attack. There are very few cases of this type of rheumatism, frequently recurring in one individual, that he has investigated without finding evidence of the development of a rather serious cardiac lesion in one of the first, if not the very first, attacks. In what way this operates to bring about subsequent attacks of rheumatism Dr. Stengel did not know, but he believes greater attention to the circulatory conditions of these individuals would prevent recurrence. Dr. Stengel also considers as an important factor in the treatment of the disease enforced rest, and he has sometimes treated cases with the actual application of plaster casts or various other forms of

fixation casts, through acute attacks and found there was a remarkable subsidence of fever and local symptoms in some cases which seemed to be uncontrollable before. It has been shown, he said, that the salicylate treatment does not cut short the duration of the disease or reduce the frequency of the cardiac complications. Indeed, it is claimed that cardiac complications are rather more frequent. Undoubtedly, whatever of specific value there is in the salicylates, the most striking manifestation is in the control of pain. With control of pain there is a greater tendency to free use of the joints. Though the patient does not get out of bed, he may use his joints in a thousand ways while supposedly at rest in bed, and the attrition of the synovial members, in which the bacteriologists have shown that bacteria are prone to lurk, may cause their dissemination. The bacteriologists, in aspirating fluid from the joints for the purpose of culture, have often been surprised to find it sterile. The explanation at first seemed difficult to find if rheumatism is, indeed, an infectious process, but it was later discovered that bacteria were present in the synovial tissues, and that the fluid in the joints was sterile, for the same reason that the edematous fluid surrounding any infectious focus (as a bacterial embolus in a small vessel in a solid tissue) may be sterile, whereas the bacteria themselves are at the very center of the focus. Dr. Stengel believes that the serum treatment has possibilities, and, probably, great possibilities of development. He began the use of antistreptococcus serum quite a number of years ago, before the supposed relation of the streptococcus to rheumatism was made out; at the time when Sahli's work called attention to staphylococci as the possible cause of rheumatism. Dr. Stengel used antistreptococcus serum because no antistaphylococcic serum was available. This treatment was quite successful in some cases of the type that has been the opprobrium of medicine, that which seems to yield to none of the methods of treatment. The antistreptococcus serum, he said, seems to give an impetus toward resistance against the disease which had been lacking before.

Dr. Woods Hutchinson, New York City, raised the question whether acute articular rheumatism is not a reaction of the tissues to a large number of infections rather than to a single one. During the last two years it has been his fortune to observe some 350 cases of chronic rheumatism. Of 120 successive cases in which he was able to follow the history carefully and thoroughly, 72 were clearly traceable to an attack of acute infection, the largest number to influenza, ten or twelve to tonsillitis, then came pneumonia, typhoid fever, scarlet fever and even diphtheria. They appear to be of the same type and follow the same course, regardless of source. Of those who did not give a history of an acute infection shortly before the attack, a number gave a history of autointoxica-

tion. Several of them were able to abort attacks with calomel and soda, taken sufficiently early and promptly.

A second question Dr. Hutchinson raised was as to the actual part which is played by the joint tissues in this disease. To what extent is this a true arthritis? He believes that one of the greatest calamities in the discussion of this subject is in likening it to gonorrheal rheumatism, an entirely different affection, as different from acute articular rheumatism as is day from night. All careful observers find that it is the peri-articular tissues and not the joint proper which are chiefly affected, and Dr. Hutchinson believes that of the peri-articular tissues it is the nerve filaments that are chiefly involved, and that a post-infective neuritis plays a large rôle in the disease. The great majority of his 120 cases were chronic ones, but in most of these the pain and later the muscular wasting and anesthesia followed clearly the line and distribution of nerve trunks. In the 30 acute cases, twenty showed well-marked pain points about the joint, though often an inch or more away from the synovia and corresponding nerve-twigs, which were agonizingly sensitive to pressure, while the rest of the swollen, fiery, glossy joint was insensitive to even heavy pressure.

Dr. Louis Burckhardt, Indianapolis, Ind., has met with disappointment in the use of salicylate of soda. He has given 180 to 360 grains, in 24 hours, and has given protracted, honest rest, as much as the patient and he could stand, and still the patient has not improved. He has, however, obtained good results from the treatment of rheumatism by venous hyperemia. It is a question of technic to get good results, but it is not a difficult technic. The point is that in acute cases the bandage is left on for a long time without producing much hyperemia. In chronic cases, like tuberculosis of the joint, the bandage is applied more tightly, producing more hyperemia, more of an exudate. The bandage is left on for an hour or an hour and a half.

Dr. J. A. Lichty, Pittsburg, Pa., for four or five years has had a strong conviction that infection occurred often by way of the tonsils, and a number of these patients had their annual or semi-annual attacks of tonsillitis, followed by joint infection. They were operated on, but the tonsils were taken out by the guillotine method, and Dr. Lichty was disappointed in his results. In the last two years, however, he has advocated digging out the stumps of the tonsils between the pillars of the fauces. During the past winter those patients whose tonsils were removed absolutely, had no recurrence of the attacks.

Dr. J. N. Upshur, Richmond, Va., concurred in the statement that in many cases there is a condition of auto-infection from gastrointestinal disturbances, and that the liver is often back of that condition of autoinfection in the intestinal canal.

For some reason the liver has failed to perform its function, and a minimum amount of healthy bile is poured out into the intestine. As a result there is fermentation and infection, which produces trouble. He believes that it is due to torpid liver, digestive disturbance, and the upset condition of the vasomotor system, and through it, metabolism, and that this covers the causation in many cases of acute rheumatism. So far as the therapy is concerned, in his experience the most efficient method of treating rheumatism has been to begin by giving a dose of calomel, combining it not with bicarbonate of soda but with cascara, alain, belladonna and nux vomica. Bearing in mind the intensely acid condition both of the perspiration and the urine, Dr. Upshur has found that when he gives the patient a pure alkali, usually 10 grain doses of bicarbonate of potassium, every two hours, through a period of 36 to 48 hours, a neutral condition of the urine is produced; that the salicylates are then most efficient, and he gets relief from pain, swelling and redness, and a minimum tendency to endocarditis.

Dr. Walter H. Neilson, Milwaukee, Wis., has observed the common infection from the tonsils, and also an intense coryza preceding an attack of rheumatism, and finds that large doses of salicylate of sodium will relieve a tonsillitis and a coryza and bring about a prompt cure. He has also noticed that those men who are subject to inflammatory rheumatism are also subject to flatulence; that there is a great deal of fermentation going on in their digestive tracts. As a prophylactic, attention should be paid to the digestive tract. He believes in the use of salicylate of sodium in large doses, not the ordinary 15-grain dose, but such doses as will cause ringing in the ears and, perhaps, mild hallucinations.

Dr. Joseph E. Gichner, Baltimore, Md., in the last few years has observed in every case of acute articular rheumatism, rheumatic fever and septic fevers, in connection with other diseases, that the point of infection was most frequently in the mouth. He considers the tonsils as being secondarily, and not primarily, affected. In every case there is inflammation of a spongy gum, or carious teeth, and the patient will be relieved of symptoms of fever as soon as the mouth is attended to. Besides these very important prophylactic measures, Dr. Gichner considers the best treatment to be to carry out a line of auto-opsonic action, or of making the antitoxin by the person who has raised his own organism, by the Bier stasis or induced hyperemia in joint inflammation.

Dr. John A. Witherspoon, Nashville, Tenn., referred to a child who had rheumatism, with tonsillar trouble invariably preceding. The tonsil was removed without any result, but when it was removed thoroughly, the child did not have any more rheumatic trouble. The same occurrence took place in

the case of another child. Dr. Witherspoon does not believe that rheumatic infection enters only through the tonsil, although the tonsil is a prolific source. He sounded a note of warning in regard to the enormous doses of salicylate of soda advised. He has had two cases of salicylate of soda poisoning. If, he said, ordinary doses of salicylate of soda do not effect in rheumatic trouble, something else should be tried. In Dr. Witherspoon's opinion the best treatment for articular rheumatism is rest, absolute rest, and that the reason cardiac complications occur more frequently is simply because the salicylate relieves the pain and the patients assume the upright position too soon and get around. Another point is to make these patients comfortable, and Dr. Witherspoon knows of nothing that gives more comfort than fixation of the joint and applications of heat.

Dr. George Dock, Ann Arbor, Mich., called attention to some observations of Aschoff made within the last three years. Aschoff described, as occurring in rheumatism, certain miliary nodules in the heart which he considers specific, histologically, which are likely to be closely associated with the fibers coming from the auriculo-ventricular bundle, and, hence, with the action of the muscle fibers.

As to the amount of salicylic acid and the salicylates, Dr. Dock said, the word specific is a very unsatisfactory one, but we must admit that the salicylates have certain effects. He believes that the salicylates have an effect of some kind, perhaps only symptomatic, even in a gonorrheal arthritis and in infections of unknown kinds. We would appreciate the action of salicylic acid better, he continued, if we realized that salicylic acid is inimical to many of the germs found in this disease group, and that salicylic acid and its salts are excreted into the tissues so likely to be affected by rheumatism or septic diseases, namely in the serous tissues. It was shown by O. Rovenbach, and Dr. Dock has often confirmed the observation, that if a patient with acute arthritis is given a salicylate, that salicylate can be recovered from the joint fluid. An iodid given to such a patient will not be found in the joint fluid. Further, in regard to salicylates, Dr. Dock pointed out that the choice of a preparation is subject to a great many individual differences. Some patients can take large doses of salicylic acid when they can not take aspirin. Aspirin is new, however, and will probably develop some drawbacks after it is used longer, as has salicylic acid. Dr. Dock also warned against enormous doses of salicylates. He, too, has seen very serious results from 240 or 360 grains given within 36 hours.

In regard to the use of blisters, Dr. Dock said it was once his fortune to apply blisters under a very experienced and venerable preceptor, and he probably has used as large and

fine blisters as anyone now living, getting blisters 9x9 for pleurisy, smaller ones over the heart and keeping up the effect with croton oil. He has seen serious results follow them; they are extremely painful and produce secondary infection. Smaller, "flying" blisters have been disappointing also, and he suggested to anyone who uses blisters to put on next time an icebag instead.

DR. NORMAN BRIDGE, Los Angeles, Cal., protested against generalizing from insufficient data. It is absurd, he said, to attempt to decide definitely in a matter of this sort from a few cases. No generalizations can be made short of hundreds of cases, even though most carefully studied. Another point is, the patient likes to be relieved from pain, he begs for it, the doctor is complimented if he can relieve it, ergo he must relieve it. Salicylates of various salts have been shown to be useful to relieve pain. Therefore they are given in very small to enormous doses. The patient is pleased to be relieved from pain; but that is of the smallest relative consequence. The patient can endure the pain not unprofitably; people do not die of pain. He can not afford to have an endocardial lesion the rest of his life. All the evidence shows that these patients recover from the joint affections. They recover if nothing is done for them. The local applications of heat, etc., are useful, perhaps, and the use of congestion produced artificially to increase the opsonic power is good enough, but the joint lesions recover spontaneously; they do not suppurate; they do get well. If the patient does not escape a heart lesion, he is usually left crippled more or less for life. The important thing in treatment is to do the thing that will lessen the danger of that permanent and life-long injury. If salicylates do nothing, are incapable of doing anything to relieve or prevent, then they are of very small consequence. Morphia and other anodyne drugs would do as well as they. If, Dr. Bridge said, as hinted by Dr. Stengel, it is true, or anywhere near true, that the patient is more likely to have a heart lesion with the use of salicylates, then they should be banished from our armamentarium. If it is true, that the alkalies lessen the tendencies to heart complication, then that is the only treatment that is worthy of any serious consideration.

DR. W. S. THAYER, Baltimore, stated that it is common to regard slight rapidity of the pulse and a soft systolic murmur as an evidence of endocarditis. It is exceedingly common, in the course of typhoid fever, for exactly similar symptoms to develop, and they are almost never regarded as an evidence of endocarditis, because endocarditis is rare in typhoid fever and common in acute polyarthritis. Dr. Thayer suggested that these symptoms might be caused by an acute endocarditis, if it is a vegetative endocarditis, or by marked defect in the valve. It is very unlikely to be caused by the ordinary kind

of endocarditis which occurs in rheumatism. The minute nodules along the mitral valve could not produce a systolic murmur. This, then, in most instances, means that there is a slight mitral insufficiency and that it is due to changes in the heart muscle. It may or may not be associated with the endocarditis. It may be associated with a grave myocarditis, which is going to produce very slight effects, but this can be told only by watching and following the case afterward. The only way to find out what acute polyarthritis has done is by following the cases for months or years. One should never allow a case of acute polyarthritis to pass out of his hands without making arrangements to see that patient months afterward, even if there are no signs of cardiac defect.

Dr. Thayer stated that the tonsils are removed because they are believed to be a very common seat of infection from which absorption occurs. It is manifestly absurd, however, he continued, to think much can be done by cutting out tonsils with the guillotine. Anyone who has seen them operated on in that way will be convinced of the necessity of having them removed entirely afterward. The stumps which remain contain the most extensive foci. As to large doses of salicylate of sodium, Dr. Thayer was of the opinion that anyone who has ever had a case of good lively maniacal delirium in cases of polyarthritis treated by too large doses of salicylate of sodium will always leave very careful rules when prescribing it afterward. Dr. Thayer gives the salicylates to relieve pain and until the ears get red.

Dr. Allen Jones, Buffalo, N. Y., said that experience leads one to believe that the cases under discussion are due to ordinary streptococcus infection. He has seen an alveolar abscess followed by a typical attack of so-called rheumatism, and acute tonsillitis is not uncommonly followed by rheumatism, in which cases throat cultures show almost a pure staphylococcus or streptococcus infection. But, he said, there is one decided difference between some cases of polyarthritis and the particular joint disease which for so many years has been called acute articular rheumatism, and that is in the association of chorea. Why is it, he asked, that chorea accompanies this one joint affection? Possibly, after all, there is associated with streptococcus septicemia some special form of organism which has not yet been isolated. Dr. Jones advised strongly against overdosage of salicylates, and against the use of antipyrin, which, he said, weakens the heart and depresses it after it is already depressed by the disease.

Dr. E. M. Richardson, Camden, N. J., has been much interested in the treatment of acute rheumatism by the Bier method of hyperemic congestion. She has used salicylates in their various forms, obtaining marked relief in many cases, but she became particularly interested in the stasis therapy

of Bier after hearing one of her confrères report a number of cases in which marked benefit had been derived from this treatment after other attempts to relieve had failed. She asked what causes the sudden improvement. Does the carbon dioxid contained in the venous blood inhibit the growth of the bacteria, or does it act as an antitoxin?

DR. W. W. TOMPKINS, Charleston, W. Va., insisted on the importance of rest in the treatment of rheumatism, and urged that symptoms be treated as they occur. Where there is extreme pain, and where it will not yield to any of the various methods of treatment, he advocates the use of morphia. In many of these cases he thought that the heart troubles probably recur where the joints of the upper extremity are involved, rather than the lower. If a patient has rheumatism in the knee and in the toes and in the wrist he is much more apt to be confined to the bed than when the disease is located in the finger, the wrist and the elbow. Dr. Tompkins regretted that the general practitioner does not have more to say in these meetings, because they can give very valuable data and statistics, inasmuch as the majority of cases are being treated by the country practitioners, not by the city men.

DR. RUFUS I. COLE, Baltimore, Md., stated that while it is possible that a number of varieties of bacteria may be instrumental in causing the condition known as acute articular rheumatism, the evidence so far is convincing with respect to only one germ, the streptococcus. He pleaded for a careful bacteriologic study in all cases where conditions will permit it, more especially in the fatal cases. Dr. Cole agreed fully with Dr. Bridge regarding treatment. It is not the relief of pain in the acute cases which should worry the physician. His mind should be set on preventing those terrible sequelæ which cause hospital wards to be filled with children and young persons suffering from incurable cardiac lesions. The genito-urinary surgeons have been instrumental in teaching us one important point in the treatment of rheumatism, that is, the necessity of treating locally the portal of entry of the infection. It is almost certain, Dr. Cole claimed, that the tonsils represent at least one, and probably the most common, portal of entry. And it must be remembered that very often the patient will deny tonsillar disease, and yet on examination the crypts will be found filled with pus. The analogy between gonorrheal infection and acute articular rheumatism is striking, for at least four well authenticated cases of gonococcal pleurisy have been reported, and skin lesions in gonococcal infections are not at all uncommon.

DR. P. K. BROWN, San Francisco, Cal., emphasized the frequency of myocardial complications, but differed from Dr. Anders as to the age at which they are most commonly found. He finds that the occurrence of very severe myocarditis, such

as we find in rheumatism, accompanied by hyperpyrexia or low but long-continued fever, is essentially a thing connected with childhood. He collected from his own records 22 cases of myocarditis in children under 5 years of age, where it persisted for more than six months. He corroborated the statement made as to the necessity of dissecting out the tonsils in certain cases. There are many tonsils, he said, that protrude so far that a guillotine operation is easy and satisfactory. In other cases the tonsils may be as large or larger, and yet can not have more than the surface shaved off with the guillotine, even if the tonsil be pulled forward with forceps.

In case there have been several throat infections in such a case, Dr. Brown considers it wise to dissect out the tonsil and eliminate the possibility of further infection from that source. As to family predisposition to rheumatism in connection with its occurrence and recurrence: In looking over the report in the Massachusetts General Hospital, Dr. Brown found that 25,000 cases were admitted in ten years, and acute articular rheumatism occurred in one case in 25. In New York, among 27,000 admitted to the Roosevelt and Presbyterian Hospitals, there was one case in 16. In the Vanderbilt Clinic, rheumatic symptoms occurred in one out of 12 cases, interesting evidence of the geographic distribution of the disease. This matter of infection of the throat, Dr. Brown said, was called attention to by French authors eighty years ago. Everyone with a rheumatic tendency has convinced himself that unless the source of infection is removed there will be recurrences of the disease sooner or later, because the patients go back to the same conditions from which they came originally, the same occupations, the same exposures, with the same unhealthy and neglected throats. If salicylates in the form of salicylate of sodium do not do good in modest doses, they are not indicated in that particular case, and it is time to look for the joint trouble being due to other things on this list, or to relieve the symptoms in some other way. Dr. Cole stated that kidney complications have followed the use of aspirin (acetsalicylic acid). He has seen a case of acute nephritis following the taking of 40 grains of aspirin (acetsalicylic acid), in four doses, two hours apart.

Dr. Alexander Lambert, New York City, agreed that myocarditis occurs much more frequently early in life than it does later in life. The changes occurring later in life are of a chronic type. Dr. Lambert does not believe that the salicylates increase the cardiac involvement. In 500 cases observed by him the aortic diastolic murmur was not present in the acute involvement of the heart. Therefore, he knew that he had taken too few cases, and he cautioned against drawing conclusions too quickly. As to the salicylate treatment, he agreed with the speakers who warned against too immense doses.

He has seen intense poisoning from 100 grains. He has himself taken 100 to 150 grains and not noticed ringing in the ears. If the salicylate does not affect the patient in 48 hours, it will have no therapeutic effect. One patient will yield to one form, another to another. If analgesics are added in small doses, 5 grains of acetphenetidin, to 1/12 of morphin, the effect is more than four times greater than for either remedy alone.

DR. S. SOLIS-COHEN, Philadelphia, stated that it goes without saying that there must be beyond the general management strict individualization. Purgation by calomel, followed by an alkaline laxative, is useful at the beginning. Fixation of the joints Dr. Cohen considers highly important, whether by plaster-of-Paris or by some less rigid measure, as is his usual practice. Among the local applications which may or may not be good—there is one which was used in Dr. Cohen's wards at the Philadelphia Hospital throughout the winter; that is, saturated solution of magnesium sulphate applied on compresses to the joints, which were fixed by bandages in such a way that the evaporation from the compress went on continuously and the application was renewed as needed. It relieved pain promptly. The same measure was useful in gonorrheal arthritis. As to blisters, Dr. Cohen said that when he spoke of blisters skilfully applied, he did not refer to a blister of 81 square inches. He did not understand how that patient survived, nor would he accept a condemnation of blisters on an experience of that kind. The addition of croton oil seems to have been an unnecessary piling of Pelion on Ossa. He uses a blister one inch square, applied in the region indicated. After the first has been opened, dressed and allowed to heal, another is applied alongside; when this heals another is applied above. The effect is good. Dr. Cohen thought he could guess at its mode of action. There is probably a reflex nervous impression on the cardiovascular centers, with some obscure chemical process, increasing or hastening defensive reactions. He protested against the administration of any of the coal tar group of drugs in the treatment of acute articular rheumatism. There is no need for them. Aspirin (acetsalicylic acid), too, is dangerous; just why, he did not know. He has seen acute cardiac failure in the case of a child who was given 3 grains of aspirin. According to Dr. Cohen it has no place in the treatment of acute infections. In comparatively small doses, it is useful in chronic painful affections. As to the action of the salicylates in general, he said, the salicyl ion, in whatever form it may be introduced, appears to be a chemical antitoxin. The phenomena of acute articular rheumatism in so far as they are capable of relief by salicyl compounds will be relieved before intoxication with the drug occurs. Its administration should stop when there appears the first evi-

dence of so-called physiologic action. It must stop absolutely for the time and not be repeated until the tinnitus has disappeared.

Some persons can bear hardly one grain and some can take enormous doses. Dr. Cohen has rarely exceeded 90 grains in 24 hours. He prefers sodium salicylate above all the preparations of salicylic acid. The true or natural salt should always be specified, as the synthetic preparations contain irritant by-products and gastric disturbance is, as a rule, owing to these, rather than to sodium salicylate itself. When the patient is weak or subject to recurrences, the addition of iron to the salicylic treatment is highly useful, and may be accomplished by the pharmaceutical expedient set forth in Dr. Cohen's paper. In regard to the tonsil and the throat, he emphasized again that not only the mouth and the throat and the faucial region, but also the nose and postpharyngeal region must be looked into and treated effectively. It is probable that some varieties of the ordinarily harmless flora of these regions become pathogenic under favoring conditions in susceptible individuals.

A MIXED INFECTION WITH TERTIAN AND QUARTAN MALARIA OCCURRING IN A PATIENT WITH SYMMETRICAL GANGRENE.

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For many years the idea has existed among various observers that there is a relation between symmetrical gangrene and malaria. This relation was hardly appreciated by Raynaud[1] in his thesis, although several of his cases were malarious subjects. In Case 6, which was reported in 1837 by Marchard, the patient was a woman who had had an outbreak of the gangrene six weeks after an attack of tertian malaria. Likewise the patient in Case 7 had had a three months' attack of tertian malaria preceding the gangrene. The patients in Cases 23 and 25 had had obscure fever. In the *New Researches* the patient in Case 1 was a malarious subject, and in Case 5 the patient had had attacks of fever. In 1869 Rey reported a case in which the patient had been affected with gangrene after attacks of intermittent fever in Senegal and later in France. In 1870 Marron reported a case in which the malaria occurred two years before the gangrene. Moursou (1873) is entitled to the credit of first claiming a relationship between the two affections.

In 1872 Raynaud, in spite of the histories of several of his cited cases, declares that he knew of no instance

1. De l'asphyxie locale et de gangrène symétrique des extrémités, Paris, 1862. Translation by Barlow for New Sydenham Society, London, 1888. Nouvelles recherches sur la nature et le traitement de l'asphyxie locale des extrémités, 1888.

where malaria was the cause of the gangrene. In 1874 Carpentier reported to the Society of Medicine a case of paroxysmal local asphyxia associated with gastric pain which occurred always at the same hour and which was only relieved by quinin. This asphyxia returned five months later and again yielded to quinin. Calmette[2] claimed that local asphyxia of the extremities may follow, accompany or precede an attack of intermittent fever. In 1877 Vaillard reported local asphyxia in a man who had had tertian fever. In 1880 Moursou[3] collected 22 cases which showed the relation of malaria to Raynaud's disease. He stated that local asphyxia often occurs after intermittent fever, especially in obstinate cases of tertian and quartan and occasionally in pernicious malaria. Petit and Verneuil[4] showed that gangrene could occur in malaria, and they cited the case of Huguier (1855) which was one of gangrene of the prepuce and part of the glans which began in an attack of intermittent fever and was attended with a slough on the upper lip. Osler[5] reported the occurrence of multiple gangrene in estivo-autumnal infections, but the lesions were not symmetrical. Chmielewsky[6] reported the case of a woman with malarial cachexia who had typical Raynaud's disease with all the stages. The patient was 23 years old and lived in Tiflis.

During the past two years in Wilmington, N. C., there has been observed a number of cases of symmetrical skin lesions. The variations have been considerable, but the perfect symmetry has predominated every case. The classification of the lesion was difficult. In many respects Raynaud's disease was simulated, but none of the cases answered the description

2. Des rapports de l'asphyxie locale des extrémités avec la fièvre intermittente paludienne, Rec. de mémoires de méd., etc., 1887.

3. Etude cliniques sur l'asphyxie locale des extrémités, Arch. d. med., November, 1880.

4. Asphyxie locale et gangrène palustres, Rev. de Chir., 1883.

5. A Case of Multiple Gangrene in Malarial Fever, Johns Hopkins Hospital Bulletin, 1900, xi.

6. Jour. d. Nerven-und psychiat. med. v, No. i, Russisch.

throughout. Dr. R. H. Bellamy had a remarkable series of cases and I am indebted to him for permission to use his notes.

CASE 1.—*History.*—The patient was a mulatto boy, aged 8, living in a very malarial neighborhood. The affection appeared in July, 1905. His parents were well and strong and there was nothing of note in the family history of either. Save malaria, the general hygienic surroundings were favorable. When seen there was found on the dorsum of each foot inflammatory areas which were symmetrical in position, shape and size. The inflammatory redness was followed by the formation of a bleb and later edema developed. The same process developed on the backs of both hands and the lower third of both forearms became edematous. Following this, the lesion next appeared beneath both eyes and later on the penis and scrotum. In each location there was edema. The temperature ranged from 100 to 102 F. Emaciation and anemia were well marked. Physical examination revealed no abnormalities.

CASE 2.—*History.*—The patient was a sister of the patient in Case 1, aged 12. In this case both feet, both hands and the skin beneath both eyes were affected symmetrically. The temperature ranged from 100 to 102 F. There were no blebs, as in Case 1. The lesion was at first moist, but later became dry, and the superficial skin was exfoliated. The patient died suddenly and a partial autopsy revealed nothing.

CASE 3.—*History.*—This patient was a brother of the two preceding patients, aged 4. The lesion was found on both hands, both feet, and beneath both eyes. As in Case 2, the lesions were moist and later became dry and exfoliated, and in this case there was sudden death.

CASE 4.—*History.*—The patient in this case was a sister of the preceding patients, aged 16. This case was characterized by a moist exfoliative condition of the skin of the last two phalanges of both middle fingers. The condition existed for two weeks and then healed spontaneously. There was no fever.

CASE 5.—*History.*—This patient was a white child, aged 4. Her previous medical history was negative except for tertian malaria. Both feet and one hand were affected with a simple dry exfoliative condition of the skin. The temperature ranged between 102 and 103 F. The child recovered.

All of these five cases of Dr. Bellamy's list occurred in the same neighborhood and at the same time. The first

four occurred in the same house. There was nothing noteworthy in the family histories, and a careful search for a cause was fruitless. The possibility of ergotism was excluded. Malaria was not expected and blood examinations were not made. Little assistance is furnished by the search for the plasmodia in such localities, as quinin is consumed so constantly by these people that the examination is worse than useless. The possibility of cold as a provocative agent was excluded by the season of the year and further by the fact that in this section extreme weather is unknown.

CASE 6.—*History.*—This patient was a girl, aged 2. She was seen through the courtesy of Dr. T. S. Burbank. The affection was a dry exfoliation of the superficial skin on the backs of both hands, symmetrical in every particular. It resembled Case 2 of Dr. Bellamy's series. Quinin had been taken when the patient was first seen and with larger doses there was recovery.

CASE 7.—*History.*—The patient whs a white man, aged 30. He was seen through the courtesy of Dr. Bellamy. There was an absence of specific history. He had been drinking beer somewhat immoderately for several months. He gave a history of repeated malarial attacks. Emaciation and anemia were marked. When first seen the patient was suffering with a violent stomatitis, strongly suggesting ptyalism. On the backs of both hands and also on the posterior surfaces of the forearms there were moist exfoliative skin lesions. The same condition existed on the back of the neck and, as was the case in the lesions of the hands and forearms, the symmetry both as to position and extent was very striking. Clinically the case was identical with the other cases, the chief point throughout being symmetry. The blood examination was negative, but this fact carries with it little weight, as the patient had probably taken enough quinin in his patent nostrums to render such a search useless. Soon after this the patient died of exhaustion. It was impossible to secure an autopsy.

In none of these cases was there any definite syncope and cyanosis. According to the classification of Monro,[7] these cases fall in his fourth class. He says this class has but a doubtful right to be called Raynaud's disease;

7. Monro (T. K.): Raynaud's Disease, Glasgow, James Maclehose & Sons.

Fig. 1.—Symmetrical lesions of the hands in Case 8 showing definite lines of demarcation; spontaneous healing far advanced; second attack in these localities.

Fig. 2. Ulcerative areas on foot and leg in Case 8: healing was spontaneous.

that "local asphyxia invades the extremities, generally without a preceding stage of syncope, and passes rapidly or slowly, but steadily, without paroxysms, on to gangrene. . . . This type occurs spontaneously or after acute fevers, and in most cases may affect more than one member of a family (Mankins,[8] Richard[9])." I am indebted to Professor Monro for his kind assistance in classifying these cases.

The studies of these cases were necessarily incomplete and would have proved of little importance had not another case come under observation which was clinically identical and which gave us a better opportunity to investigate. The case about to be described was similar in many respects to Case 2. For Case 8 I am indebted to Dr. W. D. McMillan.

CASE 8.—*History.*—The patient was a man, aged 46; his occupation that of a grocer. There was nothing of note in his previous medical history except an absence of syphilis and malaria. He was a remarkably strong, robust man. The beginning of his sickness occurred without any prodrome, with high fever which developed during the night and was followed by a profuse sweat. One week later his wife noticed that he was acting peculiarly. Among the strange things which she noticed was that he would ring his own door bell instead of using his night latch. He seemed to be dazed and was unable to attend to his business, making many absurd mistakes. There were no outbursts and no other mental changes noticed except this dazed condition and a general apathy.

For six months his condition remained unchanged. At this time his mental condition became much exaggerated and there was added to the previous symptoms utter indifference to everything. His bowels and bladder would be emptied in bed and the patient was utterly indifferent to his filthy condition. There was marked muscular weakness. Speech was slow and somewhat hesitating. There was some tremor present. The reflexes were rather sluggish. Pupils reacted to light and accommodation. The tests showed an absence of temperature sense and a great impairment of tactile sense. For the greater portion of the time the patient remained quietly in bed. On

8. Case of Spontaneous Gangrene of Toes in a Child, St. Thomas' Hos. Reports, 1882. xii. (Quoted by Monro.)

9. De la gangrène symétrique des extrémités dans la fièvre typhoïde, Union Méd., 1880, xxix. (Quoted by Monro).

the back of each hand was present a spot of exfoliating skin. These two spots were symmetrical in position, shape and size. The process was practically over at this time. The patient told me that during the preceding month he had had several chills, for which he had taken quinin. This was nine months after beginning of his affection. About three months later, Oct. 27, 1905, he was admitted to the James Walker Memorial Hospital, Wilmington, N. C. At this time the whole of the posterior surfaces of both hands were affected with a dry exfoliative lesion extending from the tips of the fingers to two inches above the wrist joints and the lines of demarcation were perfectly symmetrical in position and direction (Fig. 1). The finger tips were considerably atrophic, corresponding in this regard to the classical description of Raynaud's disease. The lesions were painless. On the external surface of the right leg, involving the lower third of the lower leg and the external surface of the foot, was a large moist ulcerative area penetrating to the muscle (Fig. 2). On the left leg was a much smaller area of the dry exfoliative variety. This leg manifested at times the appearance of a local syncope, becoming cold and apparently bloodless, and again it would become cyanotic. As the chart shows (Fig. 3), the temperature at this time and for a period certainly of three weeks, never rose above 99.6 F. There was an absence of chills. The heart, lungs, kidneys and liver were negative on examination. There was a simple secondary anemia and no leucocytosis. There was nothing suggestive of malaria, and yet during these three weeks the blood was loaded with tertian parasites in all stages of development. According to Craig the latent malaria is often characterized by organisms in all stages. Latent malaria in the southern states is practically unknown. In the routine examination of the blood for malarial parasites this is the only case found out of several hundred examinations. In spite of the presence of the parasites in the blood the temperature remained practically normal and the lesions progressed favorably.

November 29 the temperature rose without any preceding evidence of a chill to 104 F. The blood at this time contained numerous quartan parasites and also some tertian, though the former predominated. The blood was examined every two hours and no quinin given. Two hours after the rise of temperature the blood contained many large non-pigmented tertian parasites and only a few young quartans. Two hours later, or at 8 p. m., both varieties were abundant, but the quartan probably predominated. At 10 p. m. the number of tertians

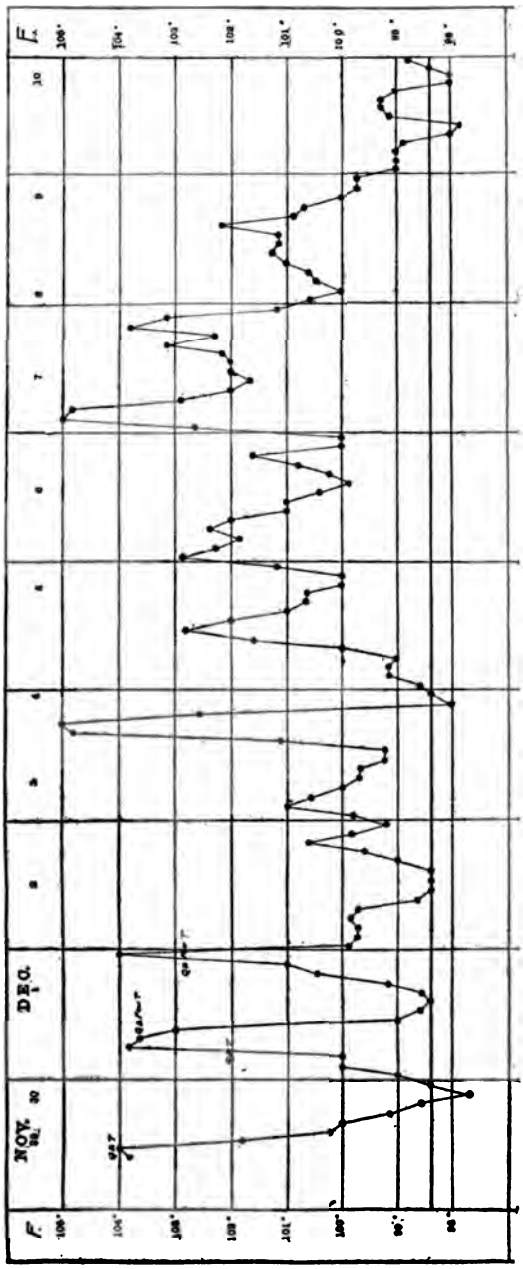

Fig. 3.—Temperature chart of patient in Case 8.

was small. At 12, midnight, the number of each variety was about the same. At 4:30 p. m., or 24 hours after the first high temperature rise, there were found full-grown tertian and quartan parasites. At 6:30 p. m. the temperature reached the second high point(103.8 F.). At this time the number of quartans was large and only a few tertians could be found. At 2:30 a. m. there was only an occasional quartan and a considerable number of tertians. At this time the temperature was normal. At 2:30 p. m. the temperature was rising for the third consecutive day, and the blood showed abundant quartan and relatively few tertian parasites. It is evident by comparing the blood findings with the chart that these three rises occurred at a time when the quartan organisms predominated. If these were due to the activity of the quartan parasites there must have been present three different broods of organism. The chart shows after the third rise of temperature an interval of moderate temperature, with a rise on the fourth day to 105 F. This would indicate a single quartan infection. Following this rise is another interval of irregular temperature, ranging from 100 to 103 F, with a rise on the fifth day again to 105 F.

At this point quinin was given hypodermically. The response was prompt and the patient was then given iron and arsenic. For a period of 40 days there was no fever, no skin lesions, and a decided improvement in the mental condition. After this interval of normal or sub-normal temperature the patient suffered a relapse. It was my misfortune to have been away at the time, but I returned in time to secure an autopsy which confirmed the idea of a relapse, as the vessels of the brain, liver and spleen were filled with parasites and pigment. I was able to find only the quartan parasites. Unfortunately, the specimens were all preserved in formalin, which interfered seriously with the histologic study.

To refer to the first febrile period there was a seldom a time when the blood was entirely free from tertian parasites, and yet the quartan parasites were undoubtedly responsible for the high temperature. Thayer[10] says that "the clinical manifestations in combined infections are dependent on the one or the other variety of parasites and a complicated fever chart resulting from the combined action of both organisms is extremely

10. Lectures on the Malaria Fevers, 1897, D. Appleton & Co., New York, and in Allbutt and Rolleston's System of Medicine, 1907.

rare." The tertian organisms seemed to play as small a part in the production of fever as they did before the appearance of the quartan parasites. In fact, the tertian element seemed to be latent throughout and the chart was apparently shaped by the quartan activity entirely. Di Mattei made the observation that if a malarial subject is inoculated with the blood of a patient suffering from another type of malaria the old infection gives way to the new. His experimentation was done on a patient suffering with quartan malaria and the inoculated organisms were estivo-autumnal. This observation hardly holds in the case in question, as the original tertian organisms remained present throughout the quartan activity.

According to Di Mattei, R. Koch and Ruge, there is in the blood a conflict between the different types of malaria. Why they can not live together is a question. W. Schewiakoff[11] says that between the protozoa there is a constant battle for existence and such a state may be assumed between the different kinds of malarial parasites. Marc[12] is inclined to think that in a question of comparison the tertian is better adapted than the quartan because of its more rapid reproduction, and that the latter is supplanted by a hyperproduction of the tertian. This idea is not carried out in this case, because the tertian was present before the appearance of the quartan and the tendency was rather for the quartan to supplant the tertian. So far there is no satisfactory explanation.

The co-existence of tertian and quartan malaria is very unusual, and so far I have been unable to find any record in the literature of any cases in this country. Golgi, in 1889, first mentioned the subject and reported a case in which the quartan parasites were first found. There were present three generations, and for ten days there was a daily paroxysm. Later tertian organisms

11. Zur Protozaenbiol. Memorien der Akademie der Wissenschaften,' St. Petersburg, 1894, lxxv, Beilage Nr. I Russisch.
12. Die Malaria im Tukestan, parasitologisch Klinisch Studien, Zeitschr f. Hyg. u. Infectionskrankh., Leipzig, 1903, xlv.

appeared in the blood producing a condition independent of the quartan. In 1890 P. Canalis mentioned the combination of tertian and quartan. In 1895 Vincenzi reported two cases of the combined infection. One of these cases was a woman, 48 years old, who had had malaria for four years. This case showed the influence of both varieties of organisms on the temperature chart differing somewhat from my case, in which the tertian played no part in the febrile movement. The most complete description of a case of the combined infection is by Marc. The case was found in Turkestan. The chart in this case differs materially from the chart of my case. In three temperature rises the quartan organisms were found, while in three others the tertian, and between these two was a rise with blood findings showing the presence of both varieties. Marc says that "when one takes into consideration that the quartan parasites complete their development in the peripheral blood principally and the tertian in the internal organs (Mannaberg), it is clear that the disappearance of the quartan from the peripheral blood was no accident; they were supplanted by the tertian." Again, in our case we have the reverse condition.

As to whether or not the mental condition in this patient can be ascribed to malaria is a question. His mental symptoms appeared after a fever that we can reasonably assume to have been malarial. I am indebted to Dr. H. A. Cotton, of the Danvers Insane Hospital, for the report on the brain. Unfortunately the whole brain and cord had been hardened and preserved in formalin. Dr. Cotton says:

I was able to get a fairly good stain, enough to make a diagnosis, or, rather, no diagnosis, as the cortex showed no reaction that could be considered pathologic. The topography was unaltered and the elements of the cortex were not affected by the malarial infection. There was probably an excess of pigment in the nerve cells, which could be accounted for by the patient's age. The blood vessels appeared a trifle thickened, but the fixed cells did not seem altered or to have prolif-

erated at all and the vessels were not increased in number. There was no evidence of general paralysis or other organic affection and no evidence of cerebral syphilis. The parasites were very easily seen in the blood stream and in great numbers. The parasites were of the quartan type. There was nothing of note in the cord and peripheral nerves.

Ascoli has shown that in malarial cachectic patients there may be symptoms simulating those of chronic alcoholism with listlessness, loss of memory, the apathetic condition, tremor and slow, uncertain speech. Thayer[10] says: "The psychical phenomena are usually of a confusional type with a tendency toward hallucinatory delirium. Slow, hesitating speech, marked muscular weakness, or sometimes increased muscular excitability, with exaggerated reflexes, are common." This patient manifested many of these symptoms, but he could scarcely have been considered a malarial cachetic when the psychic disturbance appeared. Certainly the mental condition improved under quinin treatment. Cardamentis thinks that psychic disturbances are not due to the action of the parasites, but of the toxins, and that individuals of a neurotic taint are predisposed. Pasamik[13] found among 5,412 malarial subjects 106 cases with psychosis. All were cases of depression and lasted from four days to three months, except one case of persistent dementia. In none of these cases was there present a hereditary influence.

Marandon de Montyl[14] reported 27 cases of malaria causing brain disturbances. He stated that these disturbances occurred more in acute than in chronic cases and that the prognosis was not so good as is usually supposed. Further, he stated that malaria produced no specific psychosis, but merely played the part of a provocative agent.

CONCLUSIONS.

1. Malaria may be considered a direct or a provocative agent of symmetrical gangrene of the skin. The

13. Ueber Malaria Psychosen: Wien. med. Wochschr., 1897.
14. Rev. de Méd., 1903.

skin lesion differs somewhat from the classical description of Raynaud.

2. Tertian and quartan malaria may occur simultaneously, but such a combination is exceedingly rare. Usually one type predominates.

3. Latent tertian fever occurred in Case 8. It is very unusual.

4. Certain peculiar psychoses may be present in malaria and are probably of toxic origin. This question should engage the attention of the psychiatrists in malarial districts or those having patients from these districts.

DISCUSSION.

DR. GEORGE DOCK, Ann Arbor, said that in malaria, as pointed out in 1894, the blood circulation is not uniform; the parasites gather at certain parts of the circulatory network. Further observations should be made in such cases by studying the blood from different parts of the body, not only in the extremities, but from the ear or the spleen, for the purpose of seeing how and where the parasites and leucocytes are distributed. In Dr. Dock's article, read before this Section in 1890, he described the findings in cases of latent malaria. The clinical symptoms were those of a low grade of infection of some kind and the blood showed certain parasites with a more irregular mode of development than those found in typical intermittent fever.

DR. W. S. THAYER, Baltimore, said that he had had the privilege of examining Dr. Wood's specimens. He emphasized the importance of the observations of Dr. Wood as to the frequency of symmetrical gangrene in malaria.

DR. JAMES B. HERRICK, Chicago, said that in further investigations along this line it is not only advisable to take the blood during life from different parts of the body, as suggested by Dr. Dock, but every opportunity for postmortem examination should be seized and most careful studies should be made of the changes within the vessels as well as in the vessel wall, to see if there is any blocking of the vessels with corpuscles infected with plasmodia. Apparently something of this sort was found in this case. Not only should the vessels near the seat of the lesion in the skin be studied, but the vessels of the central nervous system might show some change if careful examination were made.

PROCEEDINGS OF 1907 SESSION

TUESDAY, JUNE 4—EVENING.

The meeting was called to order at 8 p. m. in the Casino Hall, Steel Pier, by Dr. T. D. Coleman, Atlanta, Ga., chairman.

Dr. Alexander Lambert, New York City, nominated Dr. H. M. Mitchel, Atlanta, Ga., secretary *pro tem.*, who was elected.

The chairman announced the nominating committee as follows: Drs. W. S. Thayer, Baltimore; Allen A. Jones, Buffalo, N. Y., and J. A. Witherspoon, Nashville, Tenn.

Dr. John A. Lichty, Pittsburg, Pa., read a paper on "The Early and Premonitory Symptoms of Progressive Pernicious Anemia." Discussed by Drs. J. B. Herrick, Chicago; W. S. Thayer, Baltimore; T. F. Goodwin, Mt. Vernon, N. Y.; G. W. McCaskey, Ft. Wayne, Ind.; M. Einhorn, New York City; J. M. Anders, Philadelphia; N. S. Davis, Chicago; C. F. Hoover, Cleveland, Ohio; F. W. Smithies, Ann Arbor, Mich., and J. A. Lichty.

Dr. James Rae Arneill, Denver, read a paper on "Observations on Digestive Conditions in Pulmonary Tuberculosis." Discussed by Drs. W. Hutchinson, New York City; J. Daland, Philadelphia; M. J. Lichty, Pittsburg, Pa.; J. A. Witherspoon, Nashville, Tenn., and J. R. Arneill.

Dr. H. F. Harris, Atlanta, Ga., read a paper on "Investigation of the Continued Fevers of Southern Georgia." Discussed by Drs. J. A. Witherspoon, Nashville, Tenn.; E. J. Wood, Wilmington, N. C.; J. A. Lichty, Pittsburg, Pa.; A. Lambert, New York City; M. H. Fussell, Philadelphia, and H. F. Harris.

WEDNESDAY, JUNE 5—MORNING.

This session was a joint meeting with the Sections on Surgery and Anatomy and on Pathology and Physiology, devoted to a symposium on exophthalmic goiter.

"Physiology of Exophthalmic Goiter," by Dr. S. P. Beebe, New York.

"Pathology of Exophthalmic Goiter," by Dr. W. G. MacCallum, Baltimore.

"Diagnosis of Exophthalmic Goiter," by Dr. L. F. Barker, Baltimore.

"Medical Treatment of Exophthalmic Goiter," by Dr. R. B. Preble, Chicago.

"Surgical Treatment of Exophthalmic Goiter," by Dr. Albert Kocher, Berne, Switzerland.

These five papers were discussed by Drs. W. S. Halsted, Baltimore; F. Billings, Chicago, and W. J. Mayo, Rochester, Minn.

WEDNESDAY, JUNE 5—AFTERNOON.

Dr. Allen A. Jones, Buffalo, N. Y., read a paper on "The Abdominal Symptoms of Thoracic Disease." Discussed by Drs. C. F. Hoover, Cleveland, Ohio; A. Stengel, Philadelphia; A. Lambert, New York City; W. S. Thayer, Baltimore; W. H. Nielson, Milwaukee, and A. A. Jones.

Dr. Arthur R. Elliott, Chicago, read a paper on "Cardiac and Vascular Accompaniments of Diabetes Mellitus." Discussed by Drs. H. S. Stark, New York City; H. Stearns, New York City, and A. R. Elliott.

"The Venous Pulse and Some of Its Applications," by Drs. L. C. Grosh, Toledo, Ohio, and Arthur R. Cushny, London, was read by the former. Discussed by Drs. G. Dock, Ann Arbor, Mich.; A. D. Hirschfelder, Baltimore; G. W. Norris, Philadelphia, and L. C. Grosh.

Dr. C. F. Hoover, Cleveland, Ohio, read a paper on "The Tone of the Respiratory Center in Tabes Dorsalis." Discussed by Drs. A. A. Jones, Buffalo, N. Y., and C. F. Hoover.

Dr. G. E. Pfahler, Philadelphia, read a paper on "The Study of the Gastrointestinal Tract by Means of the Roentgen Rays." Discussed by Drs. J. D. Steele, Philadelphia; L. C. Grosh, Toledo, Ohio; J. M. Anders, Philadelphia; J. Daland, Philadelphia; A. A. Jones, Buffalo, N. Y.; J. C. Johnson, Atlanta, Ga.; J A. Lichty, Pittsburg, Pa.; W. Hutchinson, New York City, and G. E. Pfahler.

THURSDAY, JUNE 6—MORNING.

This session was a joint meeting with the Section on Pharmacology and Therapeutics.

The chairman, Dr. T. D. Coleman, Augusta, Ga., called the meeting to order at 9:15 a. m. The meeting was devoted to the consideration of a symposium on "Acute Articular Rheumatism."

Dr. Rufus I. Cole, Baltimore, read a paper entitled "The Etiology of Acute Articular Rheumatism."

Dr. Philip King Brown, San Francisco, read a paper entitled "Symptomatology and Diagnosis of Acute Articular Rheumatism."

Dr. Alexander Lambert, New York City, read a paper entitled "The Cardiac Complications of Acute Articular Rheumatism."

Dr. N. S. Davis, Chicago, read a paper entitled "Specific Treatment of Acute Articular Rheumatism or Treatment with Salicylates."

Dr. Solomon Solis-Cohen, Philadelphia, read a paper entitled "The Prophylaxis and General Management of Acute Rheumatic Fever."

These five papers were discussed by Drs. J. M. Anders, Philadelphia; A. Stengel, Philadelphia; W. Hutchinson, New York City; L. Burckhardt, Indianapolis, Ind.; J. A. Lichty, Pittsburg, Pa.; J. N. Upshur, Richmond, Va.; W. H. Nielson, Milwaukee; J. E. Gichner, Baltimore; J. A. Witherspoon, Philadelphia; G. Dock, Ann Arbor, Mich.; N. Bridge, Los Angeles, Cal.; W. S. Thayer, Baltimore; A. Jones, Buffalo, N. Y.; E. M. Richardson, Camden, N. J.; W. W. Tompkins, Charleston, W. Va.; R. I. Cole, Baltimore; P. K. Brown, San Fancisco; A. Lambert, New York City, and S. Solis-Cohen, Philadelphia.

THURSDAY, JUNE 6—AFTERNOON.

The nominating committee made the following report: Chairman, Dr. C. F. Hoover, Cleveland, Ohio; secretary, Dr. Joseph L. Miller, Chicago; delegate, Dr. George Dock, Ann Arbor, Mich.; alternate, Dr. L. C. Grosh, Toledo, Ohio, and they were elected.

The committee to nominate an orator on medicine named Dr. W. S. Thayer, Baltimore, who was elected.

A paper on "Observations on Plague in India" (illustrated by lantern slides) was read by Dr. Judson Daland, Philadelphia.

A paper on "A Mixed Infection with Tertian and Quartan Malaria Occurring in a Case with Symmetrical Gangrene" was read by Dr. Edward J. Wood, Wilmington, N. C. Discussed by Drs. G. Dock, Ann Arbor, Mich.; W. S. Thayer, Baltimore, and J. B. Herrick, Chicago.

A paper on "The Opsonic Theory and Therapeutic Inoculation with Bacterial Vaccines" was read by Dr. G. W. Ross, Toronto. Discussed by Drs. F. P. Hollister, Scranton, Pa.; W. H. Hutchings, Detroit, and G. W. Ross.

A paper on "A Critical Estimate of the Fermentation-Specific Gravity Method of Quantitating Sugar in Diabetes" was read by Dr. Henry A. Christian, Boston. Discussed by Drs. H. Stearns, New York City; W. S. Thayer, Baltimore, and H. A. Christian.

A paper on "Prepared and Predigested Foods" was read by Dr. Graham Lusk, New York City. Discussed by Drs. S. J. Meltzer, New York City; W. S. Thayer, Baltimore; W. A. Witherspoon, Nashville, Tenn., and W. Hutchinson, New York City.

FRIDAY, JUNE 7—MORNING.

Dr. C. H. Bunting, Charlottesville, Va., read a paper on "Experimental Anemia."

A paper on "The Uncinarial Anemia of Porto Rico," by Drs. B. K. Ashford and W. W. King, of Washington, D. C., was read by Dr. Ashford.

Dr. R. Cabot, Boston, read a paper on "Differential Diagnosis of the Various Types of Anemias."

Dr. S. J. Meltzer, New York City, read a paper on "Treatment of Anemia."

These four papers were discussed by Drs. T. Potter, Indianapolis, Ind.; A. D. Atkinson, Baltimore; A. A. Eshner, Philadelphia; W. Hutchinson, New York City; A. A. Jones, Buffalo, N. Y.; S. P. Black, Los Angeles, Cal.; A. J. Hobson, Hampton, Iowa; F. Smithies, Ann Arbor, Mich.; N. Bridge, Los Angeles, Cal.; C. H. Bunting, B. K. Ashford, W. W. King, R. Cabot and S. J. Meltzer.

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